

**A. INGREDIENT NAME:**

**DILOXANIDE FUROATE**

**B. Chemical Name:**

Entamide 2-Furoate, Furamide, Furamide (Amebicide), 2-Furancarboxylic Acid, 4-((Dichloroacetyl) Methylamino) Phenyl Ester, 4-(N-Methyl-2,2-Dichloroacetamido)phenyl 2-furoate

**C. Common Name:**

Dichlofurazol, Diclofurazol, Histomibal, Miforon, Furentomin, Furamide, Furamid, Entamizole

**D. Chemical grade or description of the strength, quality, and purity of the ingredient:**

Assay            99.96%

**E. Information about how the ingredient is supplied:**

White Crystalline Powder, Odorless, Tasteless

**F. Information about recognition of the substance in foreign pharmacopeias:**

BP 1993

**G. Bibliography of available safety and efficacy data including peer reviewed medical literature:**

Botero, D. Amoebiasis. *Trans. R. Soc. Trop. Med. Hyg.*, 1967;61: 769.

Shapiro, M. M. The recurrence-rate of *Giardia intestinalis*. *Am. J. trop. Med. Hyg.*, 1967;16: 704.

Nnochiri, E. *J. trop. Med. Hyg.*, 1967;70:224.

Wolfe, M. S. Patients with non-dysenterica symptomatic intestinal amoebiasis. *J. Am. med. Assoc.*, 1973;224:1601.

Knight, R. The treatment of non-dysenterica intestinal amoebiasis. *Gut*, 1973;14:145.

Powell, S. J. Patients treated and was considered to have cured liver abscesses. *Ann. Trop. Med. Parasit.*, 1973;67:367.

Salaki, J. S. The successful treatment of a patient with *Entamoeba polecki*. *Trop. Dis. Bull.* 1990;77:51.

Bhopale, K. K., Pradhan, K. S., and Masani, K. B. Additive effect of diloxanide furoate and metronidazole (Entamizole) in experimental mouse caecal amoebiasis. *Indian Journal of Experimental Biology*. 1995;33(1):73-74.

Pehrson, P. and Bengtsson, E. Treatment of non-invasive amoebiasis. A comparison between tinidazole alone and in combination with diloxanide furoate. *Transactions of the Royal Society of Tropical Medicine & Hygeine*, 1983; 77(6):845-846.

Salaki, J. S., Shirey, J. L., and Strickland, G. T. Successful treatment of symptomatic *Entamoeba polecki* infection. *American Journal of Tropical Medicine & Hygeine*, 1979;28(2):190-193.

Wolfe, M. S. Nondysenteric intestinal amebiasis. Treatment with diloxanide furoate. *JAMA*, 1973; 224(13):1601-1604.

Huggins, D. Treatment of amebiasis. *Hospital*, 1965; 67(5):1107-1110.

## **H. Information about dosage forms used:**

Tablet

## **I. Information about strength:**

500mg 3 times daily for 5 days or 20mg/kg/daily divided into 3 daily doses for 10 days.

## **J. Information about route of administration:**

Orally

**K. Stability data:**

Melting point 114C to 116C

Stable (Hazardous Polymerization will not occur)

**L. Formulations:**

**M. Miscellaneous Information:**

**CERTIFICATE OF ANALYSIS**  
**DILOXANIDE FUROATE B.P.**  
**BATCH # E-186/95**

MFG.DATE: 08/12/1995

EXPO. DATE:07/12/2000

QUANTITY: 5 KG

|                    |  |
|--------------------|--|
| Description:       | <i>E</i> <u>White Crystalline Powder, Odorless, Tasteless.</u> |
| Solubility         | Passed   |
| Identification     | A) Positive<br>B) Positive<br>C) Positive                      |
| Melting Range      | 114° to 116°   |
| Free Acidity       | Passed   |
| Related Substances | Complies   |
| Loss on drying     | 0.34 %   |
| Sulphated Ash      | 0.038 %  |
| Assay              | <u>99.96 %</u> <i>D</i>  |

QUALITY CONTROL REPORT

CHEMICAL NAME.: DILOXANIDE FUROATE *A* \_\_\_\_\_

MANUFACTURE LOT NO.: E-186/95

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP \_\_\_/BP \_\_\_/MERCK \_\_\_/NF \_\_\_/MART. \_\_\_/CO. SPECS. \_\_\_.

1) DESCRIPTION.:

WHITE POWDER, ODORLESS.

2) SOLUBILITY.:

VERY SLIGHTLY SOLUBLE IN WATER AND ETHANOL; SOLUBLE IN CHLOROFORM.

3) MELTING POINT.:

114 C TO 116 C. *K*

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

PASSES.: \_\_\_\_\_

FAILS.: \_\_\_\_\_

COMMENTS.:

ANALYST SIGNATURE.: \_\_\_\_\_

DATE.: \_\_\_\_\_

PREPACK TEST.: \_\_\_\_\_

DATE.: \_\_\_\_\_

INITIAL.: \_\_\_\_\_

RETEST.: \_\_\_\_\_

DATE.: \_\_\_\_\_

INITIAL.: \_\_\_\_\_

----- IDENTIFICATION -----

PRODUCT #: D6413      NAME: DILOXANIDE FUROATE

CAS #: 3736-81-0

MF: C14H11CL2NO4

SYNONYMS

AMEBIAZOL \* 8073 CB \* <sup>C</sup>[DICHLOFURAZOL \* DICLOFURAZOL \* DILOXANIDE

FUROATE \* DILOXANID FUROATE \* ENTAMIDE FUROATE] \* ENTAMIDE <sup>B</sup>  
2-FUROATE \*

FURAMIDE \* FURAMIDE (AMEBICIDE) \* 2-FURANCARBOXYLIC ACID, 4- <sup>B</sup>  
((DICHLOROACETYL)METHYLAMINO)PHENYL ESTER \* FURENTOMIN \*

<sup>C</sup> HISTOMIBAL \*  
MIFORON \*

----- TOXICITY HAZARDS -----

RTECS NO: LV1821800

2-FUROIC ACID, ESTER WITH

2,2-DICHLORO-4'-HYDROXY-N-METHYLACETANILIDE

ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES  
(RTECS)

DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE  
INFORMATION.

----- HEALTH HAZARD DATA -----

ACUTE EFFECTS

HARMFUL IF SWALLOWED.

MAY BE HARMFUL IF INHALED.

MAY BE HARMFUL IF ABSORBED THROUGH THE SKIN.

MAY CAUSE IRRITATION.

TARGET ORGAN(S):

G.I. SYSTEM

THE TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY  
INVESTIGATED.

FIRST AID

IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS  
CONSCIOUS.

CALL A PHYSICIAN.

IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND

SHOES. CALL A PHYSICIAN.

IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT,  
CALL A PHYSICIAN.

IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING

THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.

----- PHYSICAL DATA -----

APPEARANCE AND ODOR

SOLID.

----- FIRE AND EXPLOSION HAZARD DATA -----

EXTINGUISHING MEDIA

WATER SPRAY.

CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.

SPECIAL FIREFIGHTING PROCEDURES

WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO

PREVENT CONTACT WITH SKIN AND EYES.

----- REACTIVITY DATA -----

STABILITY

STABLE.

HAZARDOUS POLYMERIZATION

WILL NOT OCCUR.

----- SPILL OR LEAK PROCEDURES -----

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

WEAR RESPIRATOR, CHEMICAL SAFETY GOGGLES, RUBBER BOOTS AND HEAVY

RUBBER GLOVES.

SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.

AVOID RAISING DUST.

VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.

WASTE DISPOSAL METHOD

DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A

CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.

--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---

WEAR APPROPRIATE NIOSH/MSHA-APPROVED RESPIRATOR, CHEMICAL-RESISTANT

GLOVES, SAFETY GOGGLES, OTHER PROTECTIVE CLOTHING.

MECHANICAL EXHAUST REQUIRED.

HARMFUL IF SWALLOWED.

WEAR SUITABLE PROTECTIVE CLOTHING.

TARGET ORGAN(S):

G.I. SYSTEM

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO BE

ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA ALDRICH SHALL

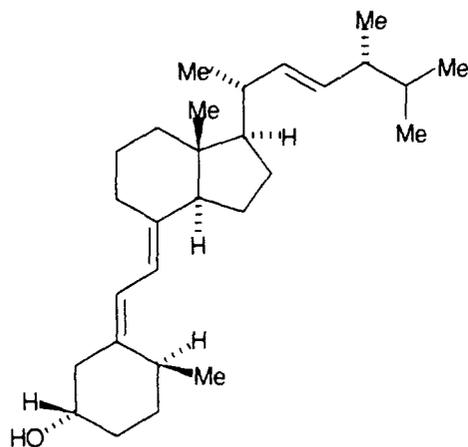
NOT BE  
HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM  
CONTACT WITH THE  
ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR  
ADDITIONAL  
TERMS AND CONDITIONS OF SALE

*dihydroergotamine tartrate* EPCRS in place of the substance being examined.

**Storage** Dihydroergotamine Tartrate should be kept in a well-closed container and protected from light.

**Action and use** Used in treatment of migraine.

## Dihydrotachysterol



$C_{28}H_{46}O$

398.7

67-96-9

**Definition** Dihydrotachysterol is (5*Z*,7*E*)-(3*S*,10*S*)-9,10-secoergosta-5,7,22-trien-3-ol.

**Characteristics** Colourless crystals or a white, crystalline powder; odourless or almost odourless.

Practically insoluble in *water*; very soluble in *chloroform*; freely soluble in *ether*; soluble in *ethanol* (96%); sparingly soluble in *arachis oil*.

**Identification** A. The *light absorption*, Appendix II B, in the range 230 to 350 nm of a 0.001% w/v solution in *methanol* exhibits three maxima, at 242, 251 and 261 nm. The *absorbance* at the maxima are 0.87, about 1.0 and about 0.65 respectively.

B. To 5 mg add 2 ml of *antimony trichloride solution* and warm in a water bath. A red colour is produced.

**Melting point** 126° to 129°, Appendix V A. It may also occur in a form melting at about 113°.

**Specific optical rotation** In a freshly prepared 2% w/v solution in *absolute ethanol*, +100° to +103°, calculated with reference to the dried substance, Appendix V F.

**Tachysterol** *Absorbance* of a 0.01% w/v solution in *methanol* at 280 nm, not more than 0.08, calculated with reference to the dried substance, Appendix II B.

**Loss on drying** When dried over *phosphorus pentoxide* at a pressure not exceeding 0.7 kPa for 24 hours, loses not more than 0.2% of its weight. Use 1 g.

**Sulphated ash** Not more than 0.1%, Appendix IX A.

**Storage** Dihydrotachysterol should be kept in an atmosphere of nitrogen, protected from light and stored at a temperature not exceeding 15°.

**Action and use** Used in treatment of hypocalcaemia.

## Dill Oil

**Definition** Dill Oil is obtained by distillation from the dried ripe fruits of *Anethum graveolens* L.

**Characteristics** A clear, colourless or pale yellow liquid, visibly free from water; odour, characteristic of the crushed fruit.

**Optical rotation** +70° to +80°, Appendix V F.

**Refractive index** 1.481 to 1.492, Appendix V E.

**Solubility in ethanol** Soluble, at 20°, in 1 volume or more of *ethanol* (90%) and in 10 volumes or more of *ethanol* (80%), Appendix X M.

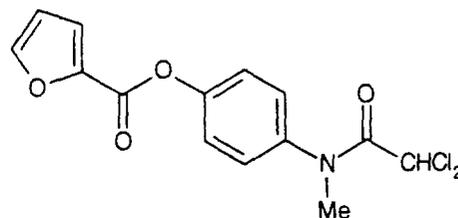
**Weight per ml** 0.895 to 0.910 g, Appendix V G.

**Content of carvone** 43.0 to 63.0% w/w, Appendix X L.

**Storage** Dill Oil should be kept in a well-filled, well-closed container, protected from light and stored at a temperature not exceeding 25°. It darkens in colour on storage.

**Action and use** Carminative.

## Diloxanide Furoate



$C_{14}H_{11}Cl_2NO_4$

328.2

3736-81-0

**Definition** Diloxanide Furoate is 4-(*N*-methyl-2,2-dichloroacetamido)phenyl 2-furoate. It contains not less than 98.0% and not more than 102.0% of  $C_{14}H_{11}Cl_2NO_4$ , calculated with reference to the dried substance.

**Characteristics** A white or almost white, crystalline powder; odourless or almost odourless.

Very slightly soluble in *water*; freely soluble in *chloroform*; slightly soluble in *ethanol* (96%) and in *ether*.

**Identification** A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of diloxanide furoate.

B. The *light absorption*, Appendix II B, in the range 240 to 350 nm of a 0.0014% w/v solution in *ethanol* (96%) exhibits a maximum only at 258 nm. The *absorbance* at the maximum is about 0.98.

C. Burn 20 mg by the method for *oxygen-flask combustion*, Appendix VIII C, using 10 ml of 1*M* *sodium hydroxide* as the absorbing liquid. When the process is complete, acidify the liquid with *nitric acid* and add *silver nitrate solution*. A white precipitate is produced.

**Melting point** 114° to 116°, Appendix V A.

**Free acidity** Shake 3 g with 50 ml of *water*, filter and wash the residue with three 20-ml quantities of *water*. Titrate the combined filtrate and washings with 0.1*M* *sodium hydroxide* VS using *phenolphthalein solution* R1 as indicator. Not more than 1.3 ml is required.

**Related substances** Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* HF<sub>254</sub> as

the coating substance and a mixture of 96 volumes of *dichloromethane* and 4 volumes of *methanol* as the mobile phase. Apply separately to the plate 5 µl of each of two solutions of the substance being examined in *chloroform* containing (1) 10.0% w/v and (2) 0.025% w/v. After removal of the plate, allow it to dry in air and examine under *ultraviolet light* (254 nm). Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

**Loss on drying** When dried to constant weight at 105°, loses not more than 0.5% of its weight. Use 1 g.

**Sulphated ash** Not more than 0.1%, Appendix IX A.

**Assay** Dissolve 0.3 g in 50 ml of *anhydrous pyridine* and carry out Method II for *non-aqueous titration*, Appendix VIII A, using 0.1M *tetrabutylammonium hydroxide VS* as titrant and determining the end point potentiometrically. Each ml of 0.1M *tetrabutylammonium hydroxide VS* is equivalent to 32.82 mg of  $C_{14}H_{11}Cl_2NO_4$ .

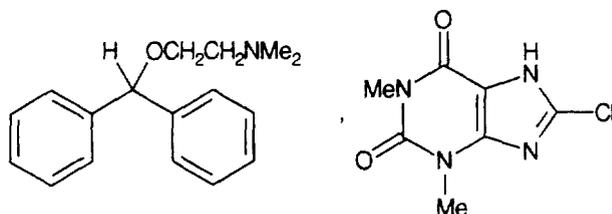
**Storage** Diloxanide Furoate should be protected from light.

### Preparation

Diloxanide Tablets

**Action and use** Antiprotozoal.

## Dimenhydrinate ☆



$C_{17}H_{21}NO, C_7H_7ClN_4O_2$  470.0 523-87-5

**Definition** Dimenhydrinate contains not less than 53.0% and not more than 55.5% of diphenhydramine (2-benzhydryloxyethyl dimethylamine,  $C_{17}H_{21}NO$ ; 255.4) and not less than 44.0% and not more than 46.5% of 8-chlorotheophylline (8-chloro-1,3-dimethylpurine-2,6(3*H*,1*H*)-dione,  $C_7H_7ClN_4O_2$ ; 214.6), both calculated with reference to the dried substance.

**Characteristics** Colourless crystals or a white, crystalline powder.

Slightly soluble in *water*, freely soluble in *chloroform* and in *ethanol* (96%); sparingly soluble in *ether*.

**Identification** Test C may be omitted if tests A, B and D are carried out. Tests A, B and D may be omitted if test C is carried out.

A. *Melting point*, 102° to 106°, Appendix V A, Method I.  
B. Dissolve 0.1 g in a mixture of 3 ml of *water* and 3 ml of *ethanol* (96%), add 6 ml of *water* and 1 ml of 2M *hydrochloric acid* and cool in ice for 30 minutes, scratching the side of the tube with a glass rod, if necessary, to initiate crystallisation. Dissolve about 10 mg of the precipitate in 1 ml of *hydrochloric acid*, add 0.1 g of *potassium chlorate* and evaporate to dryness in a porcelain dish. A reddish residue remains, which becomes violet-red when exposed to ammonia vapour.

C. The *infrared absorption spectrum*, Appendix II A, is concordant with the spectrum of *dimenhydrinate EPCRS*.

D. Dissolve 0.2 g in 10 ml of *ethanol* (96%), add 10 ml of *picric acid solution* and initiate crystallisation by scratching the side of the tube with a glass rod. The *melting point* of the precipitate, after washing with *water* and drying at 100° to 105°, is 130° to 134°, Appendix V A, Method I.

**Alkalinity** To 0.4 g add 20 ml of *carbon dioxide-free water*, shake for 2 minutes and filter. The pH of the filtrate is 7.1 to 7.6, Appendix V L.

**Clarity and colour of solution** A 5.0% w/v solution in *ethanol* (96%) is *clear*, Appendix IV A, and *colourless*, Appendix IV B, Method II.

**Heavy metals** A 10% w/v solution in a mixture of 85 volumes of *acetone* and 15 volumes of *water* complies with *limit test B for heavy metals*, Appendix VII. Prepare the standard using a lead standard solution (2 ppm Pb) obtained by diluting *lead standard solution* (100 ppm Pb) with the acetone—water mixture (20 ppm).

**Theophylline and substances related to diphenhydramine** Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel GF<sub>254</sub>* as the coating substance and a mixture of 90 volumes of *dichloromethane*, 9 volumes of *methanol* and 1 volume of 13.5M *ammonia* as the mobile phase. Apply separately to the plate 5 µl of each of three solutions in *dichloromethane* containing (1) 4.0% w/v of the substance being examined, (2) 0.020% w/v of the substance being examined and (3) 0.020% w/v of *theophylline*. After removal of the plate, dry it in a current of cold air and examine under *ultraviolet light* (254 nm). Any spot corresponding to theophylline in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3). Spray the plate with *potassium iodobismuthate solution*, allow it to dry in air and spray with *hydrogen peroxide solution* (10 vol). Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2). Disregard any spot extending from the line of application to an Rf value of about 0.1.

**Loss on drying** When dried to constant weight over *phosphorus pentoxide* at a pressure of 1.5 to 2.5 kPa, loses not more than 0.5% of its weight. Use 1 g.

**Sulphated ash** Not more than 0.2%, Appendix IX A, Method II. Use 1 g.

**Assay For diphenhydramine** Dissolve 0.2 g in 60 ml of *anhydrous acetic acid* and carry out Method I for *non-aqueous titration*, Appendix VIII A, determining the end point potentiometrically. Each ml of 0.1M *perchloric acid VS* is equivalent to 25.54 mg of  $C_{17}H_{21}NO$ .

**For 8-chlorotheophylline** To 0.8 g add 50 ml of *water*, 3 ml of 6M *ammonia* and 0.6 g of *ammonium nitrate* and heat on a water bath for 5 minutes. Add 25 ml of 0.1M *silver nitrate VS* and continue heating on a water bath for 15 minutes with frequent swirling. Cool, add 25 ml of 2M *nitric acid*, dilute to 250 ml with *water*, filter and discard the first 25 ml of the filtrate. Titrate 100 ml of the filtrate with 0.1M *ammonium thiocyanate VS* using 5 ml of *ammonium iron(III) sulphate solution R2* as indicator until the colour changes to yellowish brown. Each ml of 0.1M *silver nitrate VS* is equivalent to 21.46 mg of  $C_7H_7ClN_4O_2$ .

### Preparations

Dimenhydrinate Injection

Dimenhydrinate Tablets

**Action and use** Antiemetic.

by subcutaneous injection in addition to metronidazole 50 mg per kg daily or niridazole daily, both drugs being given for 10 days. Scragg and S. J. Powell, *Archs Dis Child*, 1973, 48, 193, per R. Knight *et al.*, *Gut*, 1973, 24, 11.

Twenty elderly patients with herpes zoster experience postherpetic neuralgia, and it completely disappeared after treatment with 60 mg given intramuscularly every 24 hours for 9 doses. In the other 6 patients pain disappeared in 2 to 4 weeks. No patients had recurrences at the end of the first week of treatment. Similar patients treated with triamcinolone experienced postherpetic neuralgia and pain more than 6 months in 4.— E. Hernandez *et al.*, 1980, 25, 424.

The hydrochloride is marketed in certain countries under the proprietary names Dametine (E. Merck) and Dehydroemetine Roche.

**Acetarsol.** Diethylamine Acetarsone; Acetarsone. The dihydrate of the diethylamine dimido-4-hydroxyphenylarsonic acid.  $C_{12}H_{11}N_2O_2$ —384.3.

**19-8 (anhydrous).**

*Specia*, In Belg.

Crystals or a white crystalline odourless powder with a slightly bitter taste. Soluble 1 in 3.5 of boiling water, and 1 in 7 of alcohol; insoluble in chloroform and ether.

Acetarsol was formerly used in the treatment of fever, relapsing fever, tropical eosinophilic dermatoses.

**19-4**

Acetarsol was formerly marketed in certain countries under the proprietary name Acetylarsan (May & Baker).

**19-5**

**19-6**

**19-7**

**19-8**

**19-9**

**19-10**

**19-11**

**19-12**

**19-13**

**19-14**

**19-15**

**19-16**

**19-17**

**19-18**

**19-19**

**19-20**

**19-21**

**19-22**

**19-23**

**19-24**

**19-25**

**19-26**

**19-27**

**19-28**

**19-29**

**19-30**

**19-31**

**19-32**

**19-33**

**19-34**

**19-35**

**19-36**

**19-37**

**19-38**

**19-39**

**19-40**

**19-41**

**19-42**

**19-43**

4777-m

**Di-iodohydroxyquinoline** (*B.P.* 1973). Iodoquinol (U.S.P.); Diiodohydroxyquin; Diiodohydroxyquinolinum; Diodoxyquinoléine. 5,7-Di-iodoquinolin-8-ol.

$C_9H_7I_2NO$ —397.0.

*CAS*—83-73-8.

*Pharmacopoeias.* In *Chin.*, *Fr.*, *Ind.*, *Int.*, *It.*, and *U.S.*

A light yellowish to tan-coloured, tasteless, microcrystalline powder, not readily wetted in water, odourless or with a slight odour.

Practically insoluble in water; sparingly soluble in alcohol, acetone, and ether. Protect from light.

**Adverse Effects.** As for Clioquinol, p.975.

Effects occasionally occurring include abdominal discomfort, diarrhoea, skin rash, acne, headache, pruritus ani, and furunculosis. Slight enlargement of the thyroid gland often occurs during treatment.

**Neurological disorders.** Reports of visual disturbances in children given di-iodohydroxyquinoline.— J. E. Etheridge and G. T. Stewart (letter), *Lancet*, 1966, 1, 261; F. E. Pittman and M. Westphal (letter), *Lancet*, 1973, 2, 566; M. M. Behrens (letter), *J. Am. med. Ass.*, 1974, 228, 693.

**Precautions.** As for Clioquinol, p.975.

Control of acrodermatitis enteropathica by di-iodohydroxyquinoline was lost in a patient when she started taking an oral contraceptive.— M. J. Jackson, *J. clin. Path.*, 1977, 30, 284.

**Absorption and Fate.** Di-iodohydroxyquinoline is partly and irregularly absorbed from the small intestine.

Following a 300-mg dose of di-iodohydroxyquinoline, 6 healthy men excreted a mean of 4.6% of the dose in the urine as glucuronide during the following 10 hours.— L. Berggren and O. Hansson, *Clin. Pharmac. Ther.*, 1968, 9, 67.

**Uses.** Di-iodohydroxyquinoline acts principally in the bowel lumen and is used alone or with metronidazole in the treatment of intestinal amoebiasis, chiefly for cyst-passers. It has been used to supplement emetine or with chloroquine and tetracycline in amoebic dysentery. It has also been used in balantidiasis and giardiasis and has been used locally against *Trichomonas vaginalis*. Di-iodohydroxyquinoline has been used in the treatment of acrodermatitis enteropathica; it is reported to act by altering zinc absorption.

The usual dosage in the treatment of amoebiasis is 600 mg thrice daily for 20 days; for children the usual dose is 10 mg per kg body-weight thrice daily. It can be employed in ambulatory patients and asymptomatic carriers.

Most of 55 patients with ocreiform atrophy and superimposed dermatitis of the anterior surface of the lower leg responded well to an ointment containing di-iodohydroxyquinoline 3% and salicylic acid 2% in Emulsifying Ointment.— A. R. H. B. Verhagen and J. W. Koten, *Br. J. Derm.*, 1968, 80, 682.

Di-iodohydroxyquinoline should not be used for the treatment of non-specific diarrhoea or other self-limiting conditions.— *Med. Lett.*, 1974, 16, 71.

**Acrodermatitis.** A 5-month-old girl with acrodermatitis enteropathica obtained remission from diarrhoea and dermatitis when treated with di-iodohydroxyquinoline 200 mg thrice daily. She relapsed and was then given a diet of fresh whole human milk; treatment with di-iodohydroxyquinoline was continued in the same dosage. On this regimen a complete remission was obtained enabling the child to be weaned to a normal diet and treatment with di-iodohydroxyquinoline to be discontinued.— R. R. Schulze and R. K. Winkelmann, *Mayo Clin. Proc.*, 1966, 41, 334.

In acrodermatitis enteropathica di-iodohydroxyquinoline acted by increasing the gastro-intestinal absorption as well as the retention of zinc.— M. J. Jackson, *J. clin. Path.*, 1977, 30, 284. See also P. J. Aggett *et al.*, *Archs Dis Child.*, 1978, 53, 691.

**Aspergillosis.** Of 13 patients with clinical pulmonary aspergillosis all had specific precipitins in their sera and most had *Aspergillus fumigatus* in their sputum. After treatment for 20 days with di-iodohydroxyquinoline 1.5 to 1.8 g daily precipitin tests became negative in 12 and

the sputum was cleared in all those previously affected. Some patients experienced clinical benefit.— K. Horsfield *et al.*, *Thorax*, 1977, 32, 250, per *Abstr. Hyg.* 1977, 52, 1131.

**Preparations**

**Di-iodohydroxyquinoline Pessaries** (*B.P.C.* 1973). Each pessary contains di-iodohydroxyquinoline 100 mg, boric acid 65 mg, phosphoric acid 17 mg, lactose 180 mg, and anhydrous dextrose 300 mg; prepared by moist granulation and compression. They should be moistened with water before insertion into the vagina. Protect from light. *A.P.F.* has a similar formula.

**Di-iodohydroxyquinoline Tablets** (*B.P.* 1973). Di-iodohydroxyquin. Tab. Tablets containing di-iodohydroxyquinoline. Protect from light.

**Iodoquinol Tablets** (*U.S.P.*). Tablets containing di-iodohydroxyquinoline.

**Proprietary Preparations**

**Diodoquin** (*Searle, UK*). Di-iodohydroxyquinoline, available as tablets of 650 mg. (Also available as Diodoquin in many other countries).

**Embequin** (*May & Baker, UK*). (Available only in certain countries.) Di-iodohydroxyquinoline, available as tablets of 300 mg.

**Other Proprietary Names**

Dioxiquin (*Spain*); Direxide (*Austral.*, *Belg.*, *Fr.*, *Switz.*); Driociquin (*Arg.*); Floraquin (*Arg.*, *Austral.*, *Belg.*); Moebiquin (*USA*); Searlequin (*Arg.*); Yodoxin (*USA*).

A preparation containing di-iodohydroxyquinoline was formerly marketed in Great Britain under the proprietary name Floraquin (*Searle Pharmaceuticals*).

4778-b

**Diloxanide** (*B.P.C.* 1963). Diloxan; RD 3803. 2,2-Dichloro-4'-hydroxy-*N*-methylacetanilide.  $C_9H_9Cl_2NO_2$ —234.1.

*CAS*—579-38-4.

A white or almost white, odourless, tasteless, crystalline powder. Slightly soluble in water; soluble 1 in 8 of alcohol, 1 in 35 of chloroform, and 1 in 66 of ether. Protect from light.

The actions and uses of diloxanide are described under Diloxanide Furoate (below). It has been given in doses of 1.5 g daily in divided doses.

Diloxanide was formerly marketed in certain countries under the proprietary name Entamide (*Boots*).

4779-v

**Diloxanide Furoate** (*B.P.*). 4-(*N*-Methyl-2,2-dichloroacetamido)phenyl 2-furoate.

$C_{14}H_{11}Cl_2NO_4$ —328.2.

*CAS*—3736-81-0.

*Pharmacopoeias.* In *Br.*

A white or almost white, odourless, tasteless, crystalline powder. *M.p.* 114° to 116°.

Very slightly soluble in water; soluble 1 in 100 of alcohol, 1 in 2.5 of chloroform, and 1 in 130 of ether. Protect from light.

**Adverse Effects.** Flatulence, vomiting, pruritus, and urticaria may occasionally occur. Transient albuminuria has been reported.

**Absorption and Fate.** Diloxanide is readily absorbed from the gastro-intestinal tract and excreted in the faeces and urine. Diloxanide furoate is hydrolysed before absorption.

**Uses.** Diloxanide acts principally in the bowel lumen and is used in the treatment of intestinal amoebiasis. It is less effective in amoebic dysentery than in asymptomatic infection, but the furoate gives higher intestinal concentrations and is possibly more effective than metronidazole in the treatment of cyst-passers.

Diloxanide furoate is used in conjunction with chloroquine and tetracycline in amoebic dysentery and is used in the treatment of hepatic amoebiasis in conjunction with chloroquine and

orell  
J

dehydroemetine or emetine.

Diloxanide furoate is administered in a dosage of 500 mg thrice daily for 10 days. The dosage for children is 20 mg per kg body-weight daily, in divided doses, for 10 days. The course of treatment may be repeated if necessary.

Diloxanide furoate is also used concomitantly with metronidazole.

**Amoebiasis.** Diloxanide furoate 375 mg, tetracycline hydrochloride 250 mg, and chloroquine phosphate 100 mg, 4 times daily for 5 days, were given in capsules to 50 of 100 patients with dysentery due to *Entamoeba histolytica* and sometimes other parasites also. The other 50 received the same regimen without chloroquine. Children younger than 10 years received half this adult dose. The overall cure-rate for *E. histolytica* was 83%, and the efficacy of the preparations was not significantly different. Other protozoa and helminths were apparently not affected.—*D. Botero, Trans. R. Soc. Trop. Med. Hyg.*, 1967, 61, 769, per *Abstr. Wild Med.*, 1968, 42, 497.

Diloxanide furoate 375 mg, tetracycline hydrochloride 250 mg, and chloroquine phosphate 100 mg, given 4 times daily for 5 days to 50 Costa Rican schoolboys, eliminated multiple intestinal protozoal infections within 2 days of completing the course. The recurrence-rate of *Giardia intestinalis* was 25% within 30 days, but *Entamoeba histolytica* did not recur for 90 days.—*M. M. Schapiro, Am. J. Trop. Med. Hyg.*, 1967, 16, 704, per *Trop. Dis. Bull.*, 1968, 65, 766. A similar report.—*E. Nnochiri, J. Trop. Med. Hyg.*, 1967, 70, 224, per *Trop. Dis. Bull.*, 1968, 65, 129.

Diloxanide furoate administered in a dose of 500 mg thrice daily for 10 days was effective in the treatment of 12 patients who were asymptomatic cyst carriers and 52 of 65 patients with non-dysenteric symptomatic intestinal amoebiasis. Flatulence was the only significant side-effect.—*M. S. Wolfe, J. Am. med. Ass.*, 1973, 224, 1601.

Diloxanide furoate was considered to be more effective than metronidazole in the treatment of non-dysenteric intestinal amoebiasis, and to be the drug of choice for this form of the disease.—*R. Knight et al., Gut*, 1973, 14, 145.

Diloxanide furoate 500 mg given with metronidazole 400 mg thrice daily for 5 days cleared amoebic cysts from the intestine in 59 of 60 patients treated and was considered to have cured liver abscesses in 58 of them. No relapses were noted during 3 months following treatment.—*S. I. Powell et al., Ann. trop. Med. Parasit.*, 1973, 67, 367, per *Trop. Dis. Bull.*, 1974, 71, 44.

The standard regimen for the treatment of amoebiasis in American Indians in Saskatchewan was metronidazole 500 mg and diloxanide furoate 500 mg twice daily for 5 days.—*R. D. P. Eaton et al., Can. J. publ. Hlth.*, 1973, 64, Suppl., 47, per *Trop. Dis. Bull.*, 1974, 71, 360.

Of 38 Peace Corps workers with amoebiasis in Ethiopia 36 were considered free of infection 1 to 2 months after treatment with metronidazole 750 mg thrice daily for 10 days followed by diloxanide furoate 500 mg thrice daily for 10 days.—*J. L. Ey, Ethiop. med. J.*, 1977, 15, 101, per *Trop. Dis. Bull.*, 1979, 76, 80.

A report of the successful treatment of a patient with *Entamoeba polecki* infection using metronidazole and diloxanide furoate.—*J. S. Salaki et al., Am. J. Trop. Med. Hyg.*, 1979, 28, 190, per *Trop. Dis. Bull.*, 1980, 77, 51.

#### Preparations

**Diloxanide Furoate Tablets (B.P.).** Tablets containing diloxanide furoate. Protect from light.

**Furamide (Boots, UK).** Diloxanide furoate, available as tablets of 500 mg. (Also available as Furamide in Austral).

medicine in the treatment of trypanosomiasis and babesiasis. It has also been tried in human infections.

**Babesiasis.** The routine clinical use of pentamidine or diminazene aceturate in infections due to *Babesia microti* was not recommended except in patients without spleens, since normally the infection was self-limiting.—*L. H. Miller et al., Ann. intern. Med.*, 1978, 88, 200.

A patient infected with *Babesia microti* who had failed to respond to chloroquine had a rapid clinical and parasitologic response after administration of diminazene. However the patient developed Guillain-Barré syndrome after treatment and it was suggested that pentamidine might be preferable to diminazene in severe cases of human babesiasis.—*T. K. Ruebush and A. Spielman, Ann. intern. Med.*, 1978, 88, 263.

**Trypanosomiasis.** Reference to use in human trypanosomiasis.—*M. P. Hutchinson and H. J. C. Watson, Trans. R. Soc. Trop. Med. Hyg.*, 1962, 56, 227; *S. E. Temu, Trans. R. Soc. Trop. Med. Hyg.*, 1975, 69, 277; East African Trypanosomiasis Research Organisation, *Trans. R. Soc. Trop. Med. Hyg.*, 1975, 69, 278.

#### Proprietary Names

Berenil (veterinary) (Hoechst, UK); Ganaseg.

4781-f

**Emetine and Bismuth Iodide (B.P. 1973).** Emet. Bism. Iod.; EBI.

CAS — 8001-15-8.

A complex iodide of emetine and bismuth containing 25 to 30% of emetine and 18 to 22.5% of Bi. It is a reddish-orange odourless powder with a bitter acid taste. Practically insoluble in water and alcohol; soluble in acetone and, with decomposition, in concentrated acids and in alkaline solutions; practically insoluble in but slightly decomposed by dilute acids. Store in airtight containers. Protect from light.

**Adverse Effects and Precautions.** As for Emetine Hydrochloride (below).

When given by mouth emetine and bismuth iodide may cause nausea, vomiting, and diarrhoea.

**Absorption and Fate.** When given by mouth, emetine and bismuth iodide undergoes little decomposition until it reaches the small intestine, where emetine is liberated and exerts a local and systemic effect.

**Uses.** Emetine and bismuth iodide has actions similar to those of emetine hydrochloride and has been used in the treatment of asymptomatic intestinal amoebiasis. When given by mouth it is only slightly decomposed before reaching the small intestine where the bulk of the emetine is then released to give a high concentration in the intestine. It has been used with tetracycline and a luminal amoebicide such as diloxanide furoate in the treatment of severe amoebic dysentery with much tissue invasion.

The frequency with which it gives rise to unpleasant side-effects makes it unsuitable for routine therapy; patients should be confined to bed.

Emetine and bismuth iodide is usually administered in enteric-coated tablets or capsules but such preparations must disintegrate very readily in the intestine or they are valueless; when in capsules, the drug should not be suspended in an oily basis. The usual dose was 200 mg daily for 12 consecutive days if tolerated by the patient.

#### Preparations

**Emetine and Bismuth Iodide Tablets (B.P. 1973).** Emet. Bism. Iod. Tab. Tablets containing emetine and bismuth iodide. They are enteric- and sugar-coated. Store at a temperature not exceeding 25° in airtight containers.

4782-d

**Emetine Hydrochloride (B.P., U.S.P.).** Emet. Hydrochlor.; Emetini Hydrochloridum; Emetini Chloridum; Emetine Dihydrochloride; Ipecine Hydrochloride; Methylcephaline Hydrochloride; Cloridrato de Emestina. 6',7',10,11-Tetramethoxyematan dihydrochloride heptahydrate; (2S,3R,11bS)-3-Ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2-[(1R)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isouquinolylmethyl]-2H-benzo[a]quinolizine dihydrochloride heptahydrate. C<sub>29</sub>H<sub>40</sub>N<sub>2</sub>O<sub>4</sub>·2HCl·7H<sub>2</sub>O = 679.7.

CAS — 483-18-1 (emetine); 316-42-7 (hydro-

chloride, anhydrous); 7083-77 (hydrate).

**Pharmacopoeias.** In Arg., Aust., Ger., Ind., Int., It., Jug., Mex., Rus., Span., Swiss, Turk., and U.S.P. variable proportion of water of crystallization.

A white or very slightly yellow line powder with a bitter taste, yellow on exposure to light after drying.

Soluble 1 in 8 of water, 1 in 10 and 1 in 4 of chloroform; practically insoluble in ether. A solution in water in a 2% solution in water has a pH of 3. Solutions are sterilised by maintaining for 30 minutes with a bactericide. Store in airtight containers. Protect from light. The stability of emetine hydrochloride.—*Schuyt et al., Pharm. Weekbl. Ned. idem*, 1979, 114, 186.

**Adverse Effects.** Emetine causes and there may be associated with it there may be necrosis of the liver. After injection nausea, vomiting, muscle weakness, urticaria, and, more rarely, mild sensory changes. Cardiovascular effects are common and include precordial pain, dyspnoea, and hypotension. Changes in the ECG include flattening or inversion of the Q-T interval in some patients. Large doses or prolonged use may cause lesions of the heart, liver, kidneys, and skeletal muscle. Acute degenerative myocarditis may give rise to sudden cardiac death. In some patients cardiac arrest appeared after the completion of therapeutic doses.

Four patients given emetine for muscular weakness or peripheral neuropathy doses ranging from 180 to 720 mg.—*D. S. Yeoh, Singapore med. J.*, 1966, 65, 32.

**Precautions.** Emetine is contraindicated in cardiac or renal disease. It is avoided during pregnancy and given to children, except in cases of dysentery unresponsive to other drugs. It should be used with great caution in elderly patients. ECG monitoring is advised during treatment.

**Absorption and Fate.** After administration emetine hydrochloride is concentrated in the liver and spleen. Very little of the drug is secreted into the intestinal lumen. Emetine is excreted mainly in the urine, and high concentrations may persist in the urine after treatment has been discontinued.

**Uses.** Emetine, an alkaloid of the emetine hydrochloride acting principally in the liver. It is given by intramuscular injection. In the course of emetine injections and cysts disappear, but most patients later show cysts in the liver, hence become carriers. Further treatment with emetine hydrochloride in these cases is valueless.

In severe amoebic dysentery it may be given with tetracycline and an amoebicide in the intestinal lumen such as diloxanide furoate. In hepatic amoebiasis emetine may be given with chloroquine and an amoebicide in the intestinal lumen, but treatment with metronidazole is generally preferred. Doses of emetine hydrochloride larger than 60 mg daily and courses longer than 10 days or repeated

4780-r

**Diminazene Aceturate (B. Ver. C. 1965).** 1,3-Bis(4-aminidophenyl)triazene bis(N-acetylglycinate) tetrahydrate.

C<sub>22</sub>H<sub>29</sub>N<sub>9</sub>O<sub>6</sub>·4H<sub>2</sub>O = 587.6.

CAS — 536-71-0 (diminazene); 908-54-3 (aceturate, anhydrous).

A yellow odourless powder. Soluble 1 in 14 of water; slightly soluble in alcohol; very slightly soluble in chloroform and ether.

**Uses.** Diminazene aceturate has trypanocidal, babesicidal, and bactericidal properties and is used in veterinary

hydroxyquinoline has also been given in the treatment of balantidiasis as an alternative to tetra- (see p.610).

hydroxyquinoline was formerly used in the treatment of acrodermatitis enteropathica: it is reported to act by enhancing zinc absorption and has now been superseded by oral zinc therapy (see p.610).

hydroxyquinoline has antibacterial and antifungal activity and has been used topically in various skin conditions, usually together with a corticosteroid (but see under Adverse Effects p.616). It also has some antitrichomonal activity.

**Amoebic Infections.** As discussed on p.609 di-iodo-hydroxyquinoline is one of the drugs used in the treatment of intestinal amoebiasis caused by *Entamoeba histolytica* and *Entamoeba fragilis*. References to this use are given below. **Antiparasitic Drugs for parasitic infections. Med Lett Drugs** 1993; 35: 111-22.

#### Preparations

Names of preparations are listed below; details are given in Part 3.

#### Official Preparations

BP 1993: Iodoquinol Tablets.

#### Proprietary Preparations

Canada: Diodoquin; Yodoxin†; Fr.: Diresiodet; S.Afr.: Floraquin; UK: Sebaquin†; Yodoxin.

**Multi-ingredient preparations.** Austral.: Floraquin; Canada: Iodoquinol; S.Afr.: Vagarsol; Viocort; Viodor; Spain: Floraquin; USA: Ytzone.

### Diloxanide Furoate (4779-v)

Diloxanide Furoate (BANM, rINNM).

1-Methyl-2,2-dichloroacetamido)phenyl 2-furoate.

$C_{14}H_{11}Cl_2NO_4 = 328.2$ .

CAS — 579-38-4 (diloxanide); 3736-81-0 (diloxanide furoate).

Pharmacopoeias. In Br. and Int.

A white or almost white, odourless, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol and in ether; freely soluble in chloroform. Protect from light.

#### Adverse Effects

Diarrhoea is the most common adverse effect during treatment with diloxanide furoate. Vomiting, pruritus, and urticaria may occasionally occur.

#### Pharmacokinetics

Diloxanide furoate is hydrolysed before absorption from the gastro-intestinal tract. The resulting diloxanide is readily absorbed and excreted mainly in the urine; less than 10% of a dose appears in the faeces.

#### Uses and Administration

Diloxanide furoate, a dichloroacetamide derivative, is a luminal amoebicide acting principally in the bowel lumen and is used in the treatment of intestinal amoebiasis. It is given alone in the treatment of asymptomatic cyst-passers and in conjunction with an amoebicide that acts in the tissues, such as metronidazole, in patients with invasive amoebiasis. Diloxanide furoate has also been used with metronidazole in the treatment of *Entamoeba polecki* infection.

For further discussion of the management of amoebic infections, see p.609.

Diloxanide furoate is administered by mouth in a dosage of 500 mg three times daily for 10 days; children may be given 20 mg per kg body-weight daily, in divided doses, for 10 days. The course of treatment may be repeated if necessary.

#### Preparations

Names of preparations are listed below; details are given in Part 3.

#### Official Preparations

BP 1993: Diloxanide Tablets.

#### Proprietary Preparations

Austral.: Furamide†; Switz.: Furamid; UK: Furamid

**Multi-ingredient preparations.** UK: Entamizole.

The symbol † denotes a preparation no longer actively marketed

### Dimetridazole (12662-z)

Dimetridazole (BAN, pINN).

1,2-Dimethyl-5-nitroimidazole.

$C_5H_7N_3O_2 = 141.1$ .

CAS — 551-92-8.

Pharmacopoeias. In BP(Vet).

Cz. includes Dimetridazole for veterinary use only. Fr. includes Dimetridazole and Dimetridazole Mesylate for veterinary use only.

An almost white to brownish-yellow, odourless or almost odourless powder which darkens on exposure to light. Slightly soluble in water; sparingly soluble in alcohol; freely soluble in chloroform; slightly soluble in ether. Protect from light.

Dimetridazole is a 5-nitroimidazole derivative similar to metronidazole. It is used in veterinary practice for the prevention and treatment of blackhead (histomoniasis) in turkeys and other poultry and of swine dysentery, and for the prevention of hexamitiasis and trichomoniasis in game birds.

### Diminazene Aceturate (4780-r)

Diminazene Aceturate (BANM, rINNM).

1,3-Bis(4-amidinophenyl)triazene bis(N-acetylglycinate).

$C_{22}H_{29}N_9O_6 = 515.5$ .

CAS — 536-71-0 (diminazene); 908-54-3 (diminazene aceturate).

NOTE. Diminazene aceturate is often referred to by its veterinary proprietary name Berenil.

Diminazene aceturate, an aromatic diamidine derivative related to pentamidine, is an antiprotozoal agent which has been used in veterinary medicine in the treatment of trypanosomiasis and babesiosis. It has also been tried in human infections.

#### References

- Ruebush TK, Spielman A. Human babesiosis in the United States. *Ann Intern Med* 1978; 88: 263.
- Abaru DE, et al. Retrospective long-term study of effects of Berenil by follow-up of patients treated since 1965. *Trop Med Parasitol* 1984; 35: 148-50.

**Residues in the diet.** An expert committee of the FAO/WHO set a maximum acceptable daily intake of diminazene at 100 µg per kg body-weight. Recommended maximum residue limits in food resulting from veterinary use were established for cattle at 500 µg per kg for muscle, 12 000 µg per kg for liver, 6000 µg per kg for kidney, and 150 µg per litre for milk.

- FAO/WHO. Evaluation of certain veterinary drug residues in food. Forty-second report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser* 857 1995.

### Dinitolmide (12665-a)

Dinitolmide (BAN, rINN).

Dinitrotoluamide; Methyl-dinitrobenzamide. 3,5-Dinitro-*p*-toluamide.

$C_8H_7N_3O_5 = 225.2$ .

CAS — 148-01-6.

Pharmacopoeias. In BP(Vet).

A cream-coloured to light tan-coloured odourless powder. Practically insoluble in water; soluble in acetone; slightly soluble in alcohol, in chloroform, and in ether.

Dinitolmide is an antiprotozoal agent used in veterinary practice for the prevention of coccidiosis in poultry.

### Eflornithine Hydrochloride (16604-j)

Eflornithine Hydrochloride (BANM, USAN, rINNM).

DFMO.  $\alpha$ -Difluoromethylornithine Hydrochloride; MDL-71782; MDL-71782A; RMI-71782 2-(Difluoromethyl)-divornithine monohydrochloride monohydrate.

$C_6H_{12}F_2N_2O_2 \cdot HCl \cdot H_2O = 236.6$ .

CAS — 67037-37-0 (eflornithine); 96020-91-6 (eflornithine hydrochloride).

### Adverse Effects and Precautions

Reported adverse effects with eflornithine include myelosuppression producing anaemia, leucopenia, and thrombocytopenia. Some patients have experienced hearing loss and alopecia. Gastro-intestinal disturbances, especially diarrhoea, can be a problem with oral administration. Seizures have occurred in about 8% of patients given eflornithine but they may have been related to the disease rather than treatment.

**Effects on hearing.** A study in 58 patients<sup>1</sup> receiving eflornithine alone or in combination with interferon alpha for the treatment of metastatic melanoma demonstrated that hearing loss at multiple frequencies was related to the cumulative dose of eflornithine and was worse in patients with pre-existing hearing deficit.

- Croghan MK, et al. Dose-related  $\alpha$ -difluoromethylornithine ototoxicity. *Am J Clin Oncol* 1991; 14: 331-5.

**Effects on the heart.** Fatal cardiac arrest occurred in an AIDS patient with *Pneumocystis carinii* pneumonia during the intravenous infusion of eflornithine 100 mg per kg body-weight over 1 hour.<sup>1</sup> Sudden death after infusion of eflornithine had occurred in several other critically ill patients with AIDS.

- Barbarash RA, et al. Alpha-difluoromethylornithine infusion and cardiac arrest. *Ann Intern Med* 1986; 105: 141-2.

### Pharmacokinetics

Eflornithine hydrochloride is absorbed from the gastro-intestinal tract. Following intravenous administration approximately 80% is excreted unchanged in the urine in 24 hours. The terminal elimination half-life is approximately 3 hours. It is distributed to the CSF.

#### References

- Haegele KD, et al. Kinetics of  $\alpha$ -difluoromethylornithine: an irreversible inhibitor of ornithine decarboxylase. *Clin Pharmacol Ther* 1981; 30: 210-17.
- Milrod F, et al. Eflornithine concentrations in serum and cerebrospinal fluid of 63 patients treated for Trypanosoma brucei gambiense sleeping sickness. *Trans R Soc Trop Med Hyg* 1993; 87: 473-7.

### Uses and Administration

Eflornithine hydrochloride is an antiprotozoal agent which acts as an irreversible inhibitor of ornithine decarboxylase, the rate-limiting enzyme in polyamine biosynthesis; trypanosomes are more susceptible to the effects of eflornithine than humans probably because of their slower turnover of this enzyme.

Eflornithine is used in African trypanosomiasis (p.613) mainly due to *Trypanosoma brucei gambiense* and is effective in the early and more importantly in the late stage of the disease when there is central involvement. Eflornithine also has activity against *Pneumocystis carinii* (see p.396) and there are several reports of it being effective in patients whose pneumonia due to this organism failed to respond to standard treatment such as co-trimoxazole or pentamidine.

It is administered intravenously or by mouth, though diarrhoea can be troublesome with the latter route. The usual dose is 100 mg per kg body-weight every 6 hours by intravenous infusion for 14 days. Some clinicians then give 300 mg per kg per day by mouth for a further 3 to 4 weeks. Dosage should be reduced in patients with impaired renal function.

Eflornithine has antineoplastic activity, and preliminary human studies have shown some encouraging responses.

**Cryptosporidiosis.** Eflornithine has been tried in the treatment of cryptosporidiosis in AIDS patients.<sup>1</sup> Other agents used in the treatment of cryptosporidiosis are discussed on p.610.

- Rolston KVI, et al. Intestinal cryptosporidiosis treated with eflornithine: a prospective study among patients with AIDS. *J Acquir Immune Defic Syndr* 1989; 2: 426-30.

**Pneumocystis carinii pneumonia.** The treatment of *Pneumocystis carinii* pneumonia is described on p.396 where reference is made to eflornithine being studied as one of the alternative agents to co-trimoxazole and pentamidine.

#### References

Database: Medline &lt;1966 to present&gt;

| Set | Search                                | Results |
|-----|---------------------------------------|---------|
| 1   | diloxanide furoate.tw.                | 30      |
| 2   | stability.tw.                         | 54760   |
| 3   | 1 and 2                               | 0       |
| 4   | from 1 keep 2,4-5,7,12,15,17,19-21,28 | 11      |

&lt;1&gt;

Unique Identifier

97321428

Authors

Qureshi H. Ali A. Baqai R. Ahmed W.

Title

Efficacy of a combined diloxanide furoate-metronidazole preparation in the treatment of amoebiasis and giardiasis.

Source

Journal of International Medical Research. 25(3):167-70, 1997 May-Jun.

Abstract

A combined formulation of diloxanide furoate and metronidazole was used to treat amoebiasis and giardiasis (cysts and vegetative forms) in 54 patients. Of these 34 patients had amoebiasis, 19 had giardiasis and one had mixed infection. Each patient took one tablet (containing 500 mg diloxanide furoate and 400 mg metronidazole), three times daily for 5 days, and the response to therapy was checked by clinical examination and by examination of fresh stools on days 3, 5 and 10. Abdominal pain was completely relieved in 91% and 84% of patients with amoebiasis and giardiasis, respectively, while parasitic clearance was 100% in both groups. Tolerance to the drug was adequate.

&lt;2&gt;

Unique Identifier

97281374

Authors

Bhopale KK. Pradhan KS. Masani KB. Kaul CL.

Title

Additive effect of diloxanide furoate and metronidazole (Entamizole) in experimental mouse caecal amoebiasis.

Source

Indian Journal of Experimental Biology. 33(1):73-4, 1995 Jan.

<3>

Unique Identifier

96319050

Authors

Sengupta M. Sengupta O.

Title

Correlation of biological activity (therapeutic and toxic) with solvochromic properties of metronidazole, emetine hydrochloride and diloxanide furoate.

Source

Indian Journal of Biochemistry & Biophysics. 32(5):302-7, 1995 Oct.

Abstract

Goat blood, when incubated for different periods with diloxanide furoate, metronidazole and emetine hydrochloride, underwent changes in fatty acid constituents and their peroxidation products measured as malonaldehyde. These findings, together with the changes noted in the drug-lipid partition coefficient, are discussed in an attempt to correlate the lipid constitution and biological activity of the drugs.

<4>

Unique Identifier

84122526

Authors

Pehrson P. Bengtsson E.

Title

Treatment of non-invasive amoebiasis. A comparison between tinidazole alone and in combination with diloxanide furoate.

Source

Transactions of the Royal Society of Tropical Medicine & Hygiene. 77(6):845-6, 1983.

Abstract

Tinidazole (40 mg/kg body-weight in one daily dose for five days) and tinidazole (same dose) plus diloxanide furoate (20 mg/kg body-weight divided into three daily doses for 10 days) were compared as treatments for amoebiasis. The parasitic cure rates were 44 and 91% respectively. We cannot, therefore, recommend tinidazole alone in this dosage as a treatment for non-invasive amoebiasis. 6

<5>

Unique Identifier

79207050

Authors

Salaki JS. Shirey JL. Strickland GT.

Title

Successful treatment of symptomatic Entamoeba polecki infection.

Source

American Journal of Tropical Medicine & Hygiene.  
28(2):190-3, 1979 Mar.

Abstract

\*  
G The second symptomatic case of Entamoeba polecki infection, the first to respond to therapy, is reported. The patient experienced intermittent episodes of abdominal cramps, diarrhea, nausea, and malaise associated with large numbers of E. polecki cysts in the stool. Following treatment with diloxanide furoate and metronidazole, all symptoms cleared and the parasite was no longer present in the stool.

<6>

Unique Identifier

73184480

Authors

Wolfe MS.

Title

\*  
G Nondysenteric intestinal amebiasis. Treatment with diloxanide furoate.

Source

JAMA. 224(12):1601-4, 1973 Jun 18.

<7>

Unique Identifier

68126424

Authors

Botero D.

Title

Treatment of intestinal amoebiasis with diloxanide furoate, tetracycline and chloroquine.

Source

Transactions of the Royal Society of Tropical Medicine & Hygiene. 61(6):769-73, 1967.

<8>

Unique Identifier

66004858

Authors

Huggins D.

Title

[Treatment of amebiasis. Results obtained with diloxanide furoate]. [Portuguese]

Source

Revista do Instituto de Medicina Tropical de Sao Paulo.  
7(2):110-1, 1965 Mar-Apr.

<9>

Unique Identifier

66037855

Authors

Huggins D.

Title

[Treatment of amebiasis. (Results obtained with diloxanide furoate)]. [Portuguese]

Source

Hospital. 67(5):1107-10, 1965 May.

<10>

Unique Identifier

95048473

Authors

Burchard GD.

Title

[Therapy for malaria and amoebiasis]. [Review] [12 refs]  
[German]

Source

Immunitat und Infektion. 22(2):45-7, 1994 Apr.

Abstract

Treatment of malaria depends on the infecting Plasmodium species. In Plasmodium falciparum malaria the treatment also depends on whether chloroquine resistances occur and whether the course is uncomplicated or complicated. Uncomplicated cases are cared for with chloroquine and with mefloquine or halofantrine when the patient comes from areas with chloroquine resistances. Patients with complicated Plasmodium falciparum malaria must get chinine and doxycycline. A careful fluid balance is extremely important in order to prevent noncardiac pulmonary edemas. Luminal infections with pathogenic Entamoeba histolytica are treated with diloxanide furoate, luminal infections with non-pathogenic Entamoeba histolytica (= E. dispar) do not have to be treated. If differentiation is not possible, all asymptomatic cyst passers must get treatment. Patients with invasive amebiasis (amebic colitis and amebic liver abscess) have to be treated with metronidazole, followed by diloxanide furoate. [References: 12]

<11>

Unique Identifier

89279444

Authors

Di Perri G. Strosselli M. Rondanelli EG.

Title

Therapy of entamebiasis.

Source

Journal of Chemotherapy. 1(2):113-22, 1989 Apr.

Abstract

Therapy of entamebiasis is critical in that, if untreated, the disease can be fatal. Recently, a new method for differentiating pathogenic and non-pathogenic amebae has been standardized. This method relies upon the electrophoretic analysis of 4 isoenzymes which allow the identification of 20 different zymodemes. It is now widely accepted that non-pathogenic strains of *Entamoeba histolytica* are not a hazard for humans and therefore don't need therapy. As a consequence, treatment must be addressed only toward infections caused by pathogenic strains. As there are different drugs available for treating amebiasis, from a therapeutical point of view the disease must be divided into two forms: intestinal and extraintestinal. For the former, drugs which reach therapeutical levels in the gut are required. The mainstay for the treatment of asymptomatic carriage of pathogenic strains is DILOXANIDE FUROATE, a very well tolerated luminal amebicide. METRONIDAZOLE and other 5-nitroimidazole compounds such as ORNIDAZOLE are indicated for the treatment of symptomatic intestinal infections as they reach good concentrations in tissues, including the bowel where ulcerations develop. In order to ensure the clearance of amebae from the gut, a subsequent cycle with diloxanide furoate is advisable. Extraintestinal forms include amebic abscesses which can develop in many sites, but most commonly in the liver. Metronidazole and related compounds are the drugs of choice; in case of liver abscess, the addition of CHLOROQUINE is indicated because of its good concentration in tissues. A subsequent cycle with diloxanide furoate is also indicated. (ABSTRACT TRUNCATED AT 250 WORDS)

# Nondysenteric Intestinal Amebiasis

## Treatment With Diloxanide Furoate

NOTICE

THIS MATERIAL MAY BE PROTECTED BY  
COPYRIGHT LAW (TITLE 17, U.S. CODE)

Martin S. Wolfe, MD

Diloxanide furoate, an investigational, amebicidal drug in the United States, was given in a ten-day course of 500 mg three times a day. This therapy led to parasitologic and symptomatic cure in all 12 asymptomatic cyst carriers and in 52 of 65 patients with nondysenteric, symptomatic, intestinal amebiasis who had all contracted *Entamoeba histolytica* infections while abroad. Criteria for cure were the absence of *E histolytica* parasites in three complete stool examinations, one and three months following completion of treatment, and complete or marked symptomatic improvement. Excessive flatulence was a common, but the only significant side effect. The high effectiveness (83% cure rate), relative ease of administration, and minimal toxicity of diloxanide furoate indicates that this drug has numerous advantages over other primarily luminal-acting amebicides presently available in this country for the treatment of chronic amebiasis.

More than 90% of the individuals seen in our Tropical Medicine Unit, who have contracted amebiasis while traveling or living abroad, had an asymptomatic or a nondysenteric chronic or subacute form of infection. Similar findings are also reported in returnees to England and France.<sup>1,2</sup> It is much more unusual in these countries to see the fulminant dysenteric form of amebiasis in travelers, with its typical presentation of frequent bloody stools, fever, marked abdominal cramps, tenesmus, and weight loss. A spectrum of symptoms is seen with nondysenteric *Entamoeba histolytica* infections, ranging from asymptomatic and mildly symptomatic individuals with complaints of increased number of soft stools, intermittent constipation, excessive distention and flatulence, and increased fatigue to more severely infected individuals who do not have frank amebic dysentery, but show evidence of some invasion of the bowel wall as manifested by very frequent watery to mushy

stools, lower abdominal cramps, weight loss, anorexia and nausea, and marked asthenia. The asymptomatic and mildly symptomatic individuals fit most definitions of so-called chronic amebiasis, while the more severely affected individuals could be said to have a subacute type of infection. The present report concerns 100 individuals exposed to amebiasis while living or traveling outside the United States and found, upon their return to Washington, DC, to have cysts larger than 10 $\mu$ , or trophozoites fitting the definition for *E histolytica*. These people were treated with diloxanide furoate (Furamide).

A number of anilides looked promising as amebicides and one of them, dichloroacet-4-hydroxy-N-methylanilide, was selected for further investigation. Ultimately, after extensive laboratory and clinical investigations, it was marketed in Britain under the name of Entamide and received the approved name diloxanide. Further investigations were carried out to find a derivative of diloxanide which would give better results in acute as well as in chronic amebiasis. Of the many derivatives examined, the furoate ester not only gave better results in acute amebic dysentery, but in the asymptomatic condition as well; it also was less toxic than diloxanide itself. This compound was given the name diloxanide furoate. It is less

soluble than its earlier parent compound and is more slowly absorbed from the bowel and excreted from the body, thus providing a higher concentration in the bowel wall and lumen for a longer period of time. Diloxanide furoate has been used extensively outside of the United States for more than 15 years in the treatment of amebiasis, but has not been licensed in this country and is restricted by federal law to investigational use. Early studies carried out in various parts of the world with diloxamide furoate used by itself, both in indigenous populations in highly endemic amebiasis areas, and to a lesser extent in returnees from amebiasis-endemic areas to England and France, have claimed cure rates of more than 90% in the chronic forms of amebiasis and cure rates in the range of 80% in the treatment of acute amebic dysentery.<sup>1-3</sup> However, diloxanide furoate gave only a 40% cure rate and was considered inadequate treatment for acute amebic dysentery encountered in Durban, South Africa.<sup>4</sup> Other workers also consider diloxanide furoate inferior to other better-absorbed drugs in acute amebic dysentery where there is significant tissue invasion.<sup>5,6</sup>

The only previous studies of diloxanide furoate in the United States were by McHardy in 1960 who reported a 90% cure rate in asymptomatic amebiasis patients (Panel on Diarrheal Disease, clinical meeting of the American Medical Association, Washington, DC); and Most (written communication, March 1970), who used diloxanide furoate both with and without chloroquine phosphate and had cure rates between 75% and 80%. Neither of these investigators reported significant toxicity.

With its reported high effectiveness, relative ease of administration, and minimal toxic effects, diloxanide furoate appeared to have numerous advantages over other primarily luminal-acting amebicides presently available in the United

From the Tropical Medicine Unit, Office of Medical Services, Department of State, Washington, DC.

Read in part before the 20th annual meeting of the American Society of Tropical Medicine and Hygiene, Boston, Dec 3, 1971.

Reprint requests to Office of Medical Services, Department of State, Washington, DC 20520 (Dr. Wolfe).

| Follow-Up               | No. Treated | Cured† |     |
|-------------------------|-------------|--------|-----|
|                         |             | No.    | %   |
| Complete                |             |        |     |
| Asymptomatic cases      | 12          | 12     | 100 |
| Symptomatic cases       | 65          | 52     | 80  |
| Total                   | 77          | 64     | 83  |
| Incomplete (eliminated) |             |        |     |
| Asymptomatic cases      | 6           | ...    | ... |
| Symptomatic cases       | 17          | ...    | ... |
| Total                   | 23          |        |     |
| Grand total             | 100         |        |     |

\*One hundred cases treated with diloxanide furoate.  
 †Based on three negative results from complete stool examinations at one and three months after treatment (a total of six negative stools) and a complete or marked symptomatic improvement.

| Symptom                            | Pretreatment |               | Posttreatment |               |
|------------------------------------|--------------|---------------|---------------|---------------|
|                                    | Cured (52)   | Failure† (13) | Cured (52)    | Failure† (13) |
| Anorexia                           | 7            | 2             | 0             | 0             |
| Nausea                             | 6            | 2             | 0             | 0             |
| Weight loss                        | 10           | 1             | 0             | 0             |
| Mushy stools                       | 40           | 8             | 11            | 4             |
| Watery stools                      | 1            | 1             | 0             | 0             |
| Mucus                              | 4            | 1             | 0             | 0             |
| Intermittent constipation          | 11           | 2             | 0             | 2             |
| Abdominal cramps                   | 12           | 3             | 3             | 0             |
| Distention                         | 16           | 5             | 1             | 2             |
| Flatulence                         | 31           | 8             | 5             | 4             |
| Fatigue                            | 17           | 5             | 3             | 1             |
| At least one posttreatment symptom |              |               | 17            | 8             |

\*Sixty-five symptomatic cases with complete follow-up. Twelve asymptomatic cases not included.

†Based on the persistence of *E histolytica* parasites in posttreatment stool specimens.

States for the treatment of non-dysenteric forms of amebiasis. A new drug investigation application was filed with the Food and Drug Administration for diloxanide furoate, and the study to be described was carried out from June 1970 through December 1971.

### Materials and Methods

The 100 individuals in the study included 84 US foreign service employees or their dependents; all but five of these were adults, a reflection of the primarily adult population seen in the Tropical Medicine Unit of the Department of State Office of Medical Services. A further 16 adults were employees of the World Bank Group, comprising various nationalities, who reside in Washington, DC, but make frequent short trips to countries in the developing world. Eighteen patients were asymptomatic and the remaining 82 had mild to moderate symptoms from their infection.

Criteria for inclusion in the study included the finding of *E histolytica*

cysts or trophozoites or both in at least one pretreatment stool examination; the absence of severe symptoms or proctoscopic findings compatible with acute amebic dysentery; and an expectation that the patient would remain in Washington, DC, during the three-month follow-up period. However, the nature of the patients' work required sudden travel to amebiasis endemic areas during this follow-up period in some cases. Informed consent for use of an investigational drug was obtained from all patients. Pretreatment and posttreatment proctoscopic examinations were not routinely carried out.

The criterion for parasitologic cure was the absence of *E histolytica* parasites in three stool examinations carried out one and three months following the completion of treatment, for a total of six negative specimens. All stool examinations were performed by the parasitology laboratory of the Department of State Office of Medical Services. Each examination consisted of direct smears in saline and

iodine, zinc sulfate, and formaldehyde-ether concentration, and amebic culture utilizing liver-cholesterol broth. Dobell's hematoxylin-stained slides were made from any specimen containing suspicious parasites. In some cases, when patients had been suddenly reassigned or were abroad at the time of follow-up, specimens were sent to our laboratory in thimerosal-iodine-formaldehyde preservative, and direct smear and concentration technique were performed on these specimens. Complete or marked symptomatic improvement was also necessary to consider an individual to be cured.

All subjects were treated on an outpatient basis. Adults were given a course of 500 mg of diloxanide furoate three times daily for ten days and children were given 20 mg/kg of body weight daily in three divided doses for ten days.

Pretreatment and immediate posttreatment white blood cell count, hematocrit reading, and urine albumin and sediment examinations were performed by the clinical laboratory of the Department of State Office of Medical Services. Following the completion of the treatment course, patients were questioned as to the occurrence of side effects and improvement in symptoms.

### Results

Twenty-three patients did not have satisfactory results of posttreatment follow-up stool examinations and were eliminated from the study. Six of these were asymptomatic and the other 17 were symptomatic.

All 12 of the asymptomatic patients who had complete follow-up had six negative results for stool examinations and were considered parasitologically cured.

Sixty-five symptomatic patients had complete follow-up and 52 of these were considered parasitologically cured and symptomatically improved, a cure rate of 80% in this group (Table 1). Of the 13 parasitologic failures, five had complete symptomatic improvement, while at least one pretreatment symptom persisted in the remaining eight. Nine of the 13 treatment failures were manifested at the one-month follow-up examination and two of those found

positive at the three-month follow-up examination had traveled to amebiasis-endemic areas between the one- and three-month follow-up examinations. Six patients with treatment failure were given a second course of diloxanide furoate and three were cured, but *E histolytica* infection persisted in the other three. These second courses of diloxanide furoate are not included in determining cure rates.

The total cure rate obtained in the 77 patients (12 asymptomatic and 65 symptomatic) with satisfactory follow-up findings was 83% (Table 1).

In the successfully treated symptomatic group, all those with symptoms of anorexia, nausea, constipation, and weight loss, were free from these symptoms following treatment. Eleven individuals with soft stools before treatment continued to have soft stools during follow-up. Five of the 31 individuals who had had excessive flatulence still had this complaint after treatment, but only one of 16 individuals who had complained of distention continued to have this disturbance. Fatigue persisted in only three of 17 people who had had this complaint (Table 2).

Twenty-six patients who had complete follow-up had coincidental *Entamoeba hartmanni* infections before treatment, and in only two of them was this parasite present in post-treatment specimens.

A universal side effect was excessive flatulence, and 87% of those questioned as to occurrence of side effects complained of this. The only other significant side effects occurred in five patients who complained of nausea, three of anorexia, two of diarrhea, and two of mild abdominal cramps while taking the drug, but all completed the full course of treatment without incident (Table 3). No significant abnormalities were found between pretreatment and post-treatment blood cell counts and urinalyses.

### Comment

The results of this investigation, the elimination of cysts from all 12 asymptomatic patients, and an overall cure rate of 83% in the 77 diloxanide furoate-treated patients with adequate follow-up, are similar to those of the two previous studies of

|                         | Recorded | %    |
|-------------------------|----------|------|
| Flatulence              | 78       | 87.4 |
| Anorexia                | 3        | 3.3  |
| Nausea                  | 5        | 5.6  |
| Diarrhea                | 2        | 2.2  |
| Abdominal cramps (mild) | 2        | 2.2  |

\*One hundred patients treated with diloxanide furoate. Ninety were followed up and recorded and ten were in a group with no or an incomplete follow-up.

this drug in the United States by McHardy and Most (written communication, March 1970). The results are also considered comparable to those obtained in other investigations of diloxanide furoate in nonendemic amebiasis areas. In one of the early studies of diloxanide furoate at the Hospital for Tropical Diseases in London, a 95.5% cure rate was obtained in 35 patients with chronic amebiasis when given a standard ten-day course of diloxanide furoate. However, in that study the mean number of follow-up stool examinations was only 1.5<sup>2</sup>; and it is quite likely that if six follow-up examinations over a three-month period had been carried out as in the present study, the cure rate would have dropped somewhat. In another study, Felix et al<sup>3</sup> treated 54 young adults with chronic amebiasis, who had returned to France after having spent a period in Algeria, with a standard course of diloxanide furoate. Cure was claimed for all but two of these patients, but follow-up, for the most part, was accomplished for only a fortnight after the end of treatment.<sup>2</sup> Other reported trials showing a high cure rate with diloxanide furoate were carried out primarily on residents in highly endemic amebiasis areas,<sup>3</sup> and are not thought to be comparable to the present trial that was carried out in nonendemic areas where the disease manifestations differ and the risk of reinfection during follow-up is minimal.

The good result with only minor attendant side effects obtained in this study with a ten-day course of diloxanide furoate compares favorably with and in many respects is superior to other amebicides used in the United States and elsewhere in the treatment of nondysenteric amebiasis. In England, orally given emetine-bismuth-iodide is suggested as the standard of reference against other amebicides in drug trials,<sup>1</sup> but this

drug is not available in the United States and frequent troublesome side effects can occur with its use. Tetracyclines, particularly oxytetracycline (Terramycin), and tetracycline hydrochloride, usually given in a dose of 1 or 2 gm daily for ten days, are highly effective in acute amebic dysentery, but relapse rates are high.<sup>4</sup> However, when this course is combined with or followed by a 21-day course of 650 mg of diiodohydroxyquin (Diodoquin) three times a day (often this course is combined or followed with a four-week course of chloroquine phosphate to prevent later development of liver abscess), cure rates as high as 95% without relapse have been obtained in acute amebic dysentery.<sup>6</sup> There are no valid reports on the effectiveness of this combined regimen in the more chronic forms of amebiasis, but cure rates of 80% to 90% should be obtainable. However, this regimen has numerous drawbacks, including (1) a prolonged course of treatment, (2) the not infrequent occurrence of diarrhea, (3) the potential risk of bacterial and monilial overgrowth, (4) teeth discoloration in children due to the tetracycline; and (5) the potential for reactions to iodine with diiodohydroxyquin. Diiodohydroxyquin, by itself in a 21-day course, is usually well tolerated and provides cures on the order of at least 75% in chronic amebiasis,<sup>10</sup> but again there is a rather prolonged course of treatment and iodine-sensitive individuals cannot use it. Also, this drug, though to a far lesser degree than the related compound iodochlorhydroxyquin (Entero-Vioform),<sup>11</sup> has led to a few cases of optic atrophy or polyneuropathy or both with long-term administration of larger doses than recommended for treatment of amebiasis, such as in the management of acrodermatitis enteropathica.<sup>12</sup> Paromomycin (Humatin) can be given in a short course and cure rates averaging 80% have been reported, but it is more effective in acute intestinal amebiasis than in the asymptomatic carrier state.<sup>13</sup> When it is used alone, relapses are frequent, and in the required doses, it frequently causes diarrhea and other gastrointestinal complaints and can lead to a reversible malabsorption defect.<sup>14</sup> Carbarsone, an arsenical, when employed alone is curative in only

about 50% of cases.<sup>4</sup> Although it is normally well tolerated, fatalities as a result of exfoliative dermatitis, liver necrosis, or hemorrhagic encephalitis have been reported.<sup>15</sup> Glycobiarsol (Milibis), is also an arsenical and when given alone, the cure rate is disappointingly low.<sup>16</sup> Although side effects are fewer with glycobiarsol than with carbarsonne, isolated instances of arsenical toxicity have been reported.<sup>16</sup> In view of the wide range of amebicides available, it is doubtful whether arsenicals should be used for a chronic condition. Metronidazole has been heralded as the most effective drug for all forms of amebiasis. Although metronidazole has been shown to be highly effective in acute invasive forms of amebiasis,<sup>17</sup> claims that it is superior to primarily luminal-acting drugs, when used by itself in noninvasive forms of amebiasis, are not substantiated in all studies. Quite favorable results were obtained by the use of metronidazole alone in various dosage regimens in Pakistan<sup>18</sup> and India.<sup>19</sup> But studies in Bangkok<sup>20</sup> and London<sup>21</sup> showed metronidazole by itself to be much less satisfactory for the treatment of noninvasive forms of amebiasis in the lumen of the bowel. In the London study, carried out at the Hospital for Tropical Diseases, it was concluded that the cure rate in these forms of amebiasis was no higher with metronidazole in adequate doses than with diloxanide furoate alone, and side effects were more common and troublesome. It was thought that metronidazole is less effective as a luminal amebicide because it is almost completely absorbed from the small bowel and may thus only affect intraluminal amebae if they are in very close proximity to the colonic mucosa.<sup>21</sup>

A two- to four-week course of chloroquine phosphate, concomitant with or following the use of some of the drugs discussed, is often employed as a precautionary measure against the possible subsequent occurrence of amebic liver abscess.<sup>22</sup> The later development of amebic liver abscess is a rare occurrence in well-nourished, otherwise healthy individuals with nondysenteric amebiasis who comprised the subjects of the present study. Since side effects of chloroquine phosphate are frequent

and may be additive to those caused by primary bowel-active drugs, such as diloxanide furoate (or tetracyclines, metronidazole, or diiodohydroxyquin used in other studies), and since we have not encountered amebic liver abscess following the use of these drugs, chloroquine phosphate has not been used as a routine precautionary measure in the treatment of the usual noninvasive amebiasis patient in our unit.

Little is known concerning possible teratogenic effects of diloxanide furoate, and since the main indication for its use is for a nonacute condition, it appears best at this time to withhold its use at least during the early stage of pregnancy. Some investigators have shown activated charcoal to be beneficial in decreasing the only common side effect of diloxanide furoate, excessive flatulence,<sup>2</sup> but this preparation was not used in the present study.

Although diloxanide furoate by itself may not be a satisfactory treatment for acute amebic dysentery,<sup>4,5</sup> it holds great promise as a luminal amebicide in a follow-up course of treatment to metronidazole in cases of acute amebiasis, particularly if diloxanide furoate becomes licensed and readily available for treatment of amebiasis in this country. This combination of metronidazole (in a dose of 500 to 750 mg three times a day for five to ten days) followed by a ten-day standard course of diloxanide furoate, could possibly represent a near ideal regimen for acute amebic dysentery and could also possibly lead to an even higher cure rate in nondysenteric amebiasis than either drug alone. It might also prove superior to the present commonly used regimen of a course of metronidazole followed by 21 days of diiodohydroxyquin therapy, which was recently reported to have been followed by the appearance of amebic liver abscesses in five patients whose amebic colitis had been successfully treated with these two drugs.<sup>23</sup> We are presently evaluating a regimen of metronidazole and diloxanide furoate in a series of patients with more acute signs and symptoms of amebiasis than those included in the present investigation, wherein diloxanide furoate by itself has been shown to be an effective, safe, and simple regimen for the

treatment of chronic and subacute nondysenteric amebiasis.

Diloxanide furoate would therefore appear to be a valuable addition to the assortment of amebicidal drugs used in this country and it is hoped that it can be soon licensed for routine use.

#### Nonproprietary Name and Trademark of Drug

Metronidazole—Flagyl.

#### References

1. Woodruff AW, Bell S: The evaluation of amebicides. *Trans R Soc Trop Med Hyg* 61:435-439, 1967.
2. Felix H, et al: Treatment of amoebiasis with entamide furoate. *Bull Soc Pathol Exot* 55:370-379, 1962.
3. Botero D: Treatment of acute and chronic intestinal amebiasis with entamide furoate. *Trans R Soc Trop Med Hyg* 58:419-421, 1964.
4. Wilmot AJ, et al: Some newer amebicides in acute amoebic dysentery. *Trans R Soc Trop Med Hyg* 56:85-86, 1962.
5. Seaton DR: Amebicides. *Gut* 206:16-19, 1971.
6. Marsden PD, Schultz MG: Intestinal parasites. *Gastroenterology* 57:724-750, 1969.
7. Sapero JJ, Lawless DK: The "MIF" stain-preservation technique for the identification of intestinal protozoa. *Am J Trop Med Hyg* 2:613-619, 1953.
8. Woodruff AW, Bell S: Clinical trials with entamide furoate and related compounds: I. In a non-tropical environment. *Trans R Soc Trop Med Hyg* 54:389-395, 1960.
9. Powell SJ: Short-term followup studies in amoebic dysentery. *Trans R Soc Trop Med Hyg* 61:765-768, 1967.
10. Most H: Current concepts in therapy: Treatment of amebiasis. *N Engl J Med* 262:513-514, 1960.
11. Schultz MG: Entero-Vioform for preventing travelers' diarrhea, editorial. *JAMA* 220:273-274, 1972.
12. Annotations: Cloquinol and other halogenated hydroxyquinolines. *Lancet* 1:679, 1968.
13. Sodeman WA Jr: Amebiasis (clinical seminar). *Am J Dig Dis* 16:51-60, 1971.
14. Keusch GT, et al: Malabsorption due to paromomycin. *Arch Intern Med* 125:273-276, 1970.
15. Radke RA, Baroody WG: Carbarsonne toxicity: A review of the literature and report of 45 cases. *Ann Intern Med* 47:418-427, 1957.
16. Today's drugs: Drugs for dysentery. *Br Med J* 1:825-828, 1964.
17. Powell SJ: Drug therapy of amoebiasis. *Bull WHO* 40:953-956, 1969.
18. Khambatta RB: Metronidazole and the "symptomless cyst-passer." *Med Today* 3:72-74, 1969.
19. Chuttani PN, et al: The cyst passer. *Indian Practitioner* 21:714-718, 1968.
20. Chongsuphajasiddhi T, et al: Treatment of *Entamoeba histolytica* cyst passers with metronidazole. *Southeast Asian J Trop Med Public Health* 2:29-33, 1971.
21. Kanani SR, Knight R: Experiences with the use of metronidazole in the treatment of non-dysenteric intestinal amebiasis. *Trans R Soc Trop Med Hyg* 66:244-249, 1972.
22. Powell SJ, Elsdon-Dew R: Chloroquine in amoebic dysentery. *Trans R Soc Trop Med Hyg* 65:540, 1971.
23. Weber DM: Amebic abscess of liver following metronidazole therapy. *JAMA* 216:1339-1340, 1971.

## SUCCESSFUL TREATMENT OF SYMPTOMATIC *ENTAMOEBIA POLECKI* INFECTION\*

J. S. SALAKI, J. L. SHIREY, AND G. T. STRICKLAND

Department of Medicine, National Naval Medical Center and Uniformed Services  
University of the Health Sciences, Bethesda, Maryland 20014

**Abstract.** The second symptomatic case of *Entamoeba polecki* infection, the first to respond to therapy, is reported. The patient experienced intermittent episodes of abdominal cramps, diarrhea, nausea, and malaise associated with large numbers of *E. polecki* cysts in the stool. Following treatment with diloxanide furoate and metronidazole, all symptoms cleared and the parasite was no longer present in the stool.

Human infection with *Entamoeba polecki* is rare and the parasite has been confused microscopically with *Entamoeba histolytica*.<sup>1</sup> It is generally considered not to be a pathogen for man. Herein, we report a case of prolonged symptomatic *E. polecki* intestinal disease in a patient in whom medical treatment for the organism resulted in the first clinical and laboratory cure. This is the 20th human case reported, the second in which the patient had been symptomatic.

### CASE REPORT

D. McK., a 24-year-old Peace Corps volunteer, had been stationed in Upper Volta between July 1974 and June 1976, living in the back-country in open huts into which local domestic animals would freely roam. Pertinent animal contact occurred with pigs as well as with a pet monkey. Before entering the Peace Corps, he had no prior history of gastrointestinal disease. However, while in Africa, he experienced multiple episodes of dysentery diagnosed as both amebic and bacillary. With each episode he was treated with appropriate therapy and obtained temporary symptomatic improvement.

When discharged from the Peace Corps in June 1976 he again experienced abdominal pain and diarrhea and was successfully treated for hook-

worm infection. Nevertheless, he continued to have mucoid stools, diarrhea, nausea, headache, weakness, malaise, and abdominal cramps. His weight, which had been 155 lbs in June 1974, was 134 lbs 2 years later.

In September 1976 the patient was first seen at the National Naval Medical Center for investigation of his continued gastrointestinal complaints. At that time his physical examination was unremarkable, other than mucoid stool on rectal exam. A stool specimen observed for parasites showed a heavy infection with *Entamoeba polecki* and he had a 26% eosinophilia (Fig. 1).

The patient was begun on a course of metronidazole, 750 mg three times per day for 10 days and diiodohydroxyquin, 650 mg three times per day for 20 days. Although subjective improvement occurred and the parasite was absent from the stool briefly, both *E. polecki* cysts and his symptoms recurred (Fig. 2). Over the next 10 months the patient received numerous courses of treatment with anti-amebicides, with no sustained resolution of either symptoms or presence of the organism in his stool specimens, although symptomatic improvement often coincided with reductions in numbers of cysts in the feces during therapy. Extensive laboratory investigations seeking another cause of his diarrhea and or eosinophilia were normal or negative and are listed in Table 1. All routine laboratory tests were normal. A total of 31 stool specimens were examined with no other intestinal parasites observed. *Schistosoma haematobium* were not present in the urine. Repeated thick blood films did not show filariae. However, eosinophilia was always present and although it diminished after successful therapy for the *E. polecki*, it persisted (Figs. 1 and 2).

In July 1977, the luminal agent, diloxanid-

Accepted 13 September 1978.

\* The opinions or assertions contained herein are the private ones of the authors and not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

Address reprint requests to: CAPT. G. T. Strickland, MC, USN, Department of Medicine, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, Maryland 20014.

NOTICE  
THIS MATERIAL MAY BE PROTECTED BY  
COPYRIGHT LAW (TITLE 17, U.S. CODE)

Reprinted with permission  
through the Copyright  
Clearance Center

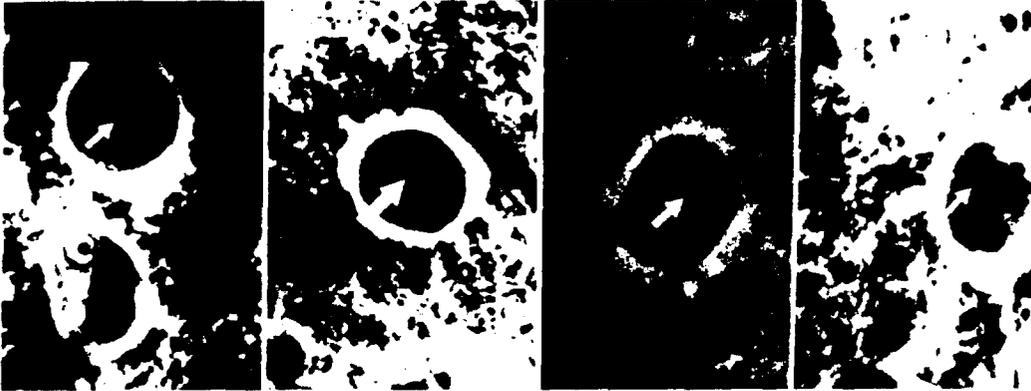


FIGURE 1. Representative *E. polecki* cysts. The karyosome is large in comparison with the nucleus and chromatin is abundant in the nuclear membrane. Chromatoid bodies are numerous (long arrow) while inclusion masses (short arrows) are seen in some cysts. Lawless and trichrome stain,  $\times 960$ .

furoate (Furamide<sup>®</sup>), was used for the first time. Following a 10-day course of metronidazole 750 mg three times per day, diloxanide furoate was given for 10 days, 500 mg three times daily. Upon completion of taking both agents, he noticed subjective improvement in his condition with resolution of abdominal cramps, more formed, less mucoid stools and improved appetite. Although he had a rare isolated stool negative for parasites associated with treatment in the prior 10 months, he has subsequently had 12 consecutive negative stool exams over the past 12 months and only rarely has a loose stool following a dietary indiscretion, e.g., excessive beer consumption.

DISCUSSION

*Entamoeba polecki* was first described and named by von Prowazek in 1912 when it was first seen by him in pigs and later monkeys, cattle, and sheep, and was named after Dr. Poleck, a Samoan physician.<sup>2</sup> The life cycle includes both trophozoite and cyst stages, although trophozoites are infrequently seen in the stool. Almost exclusively described as a parasite of pigs and monkeys, it has been found in human stools on rare occasions.<sup>1, 3-6</sup> Transmission from certain domestic animals, particularly pigs and monkeys, is the most likely source of infection, but human-to-human spread has also been suggested.<sup>6</sup>

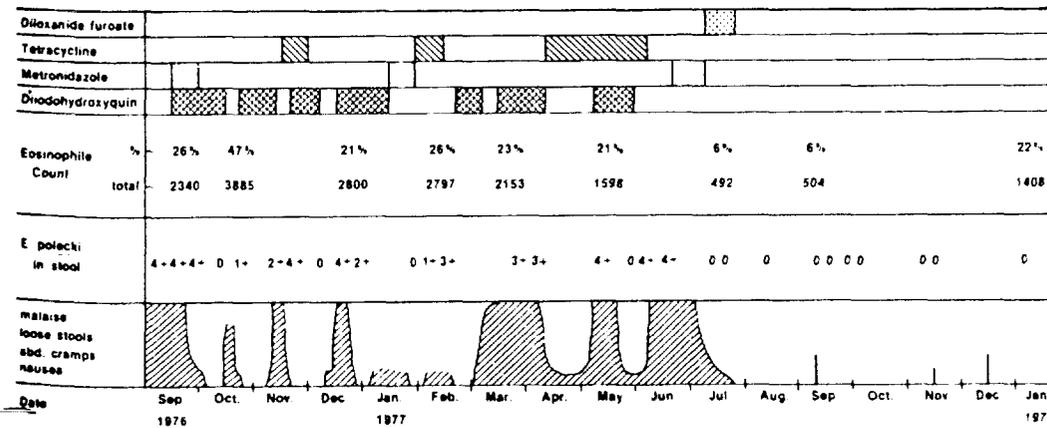


FIGURE 2. Course of illness showing symptoms, *E. polecki* cysts in stools, eosinophil count, and treatment. The patient remains asymptomatic and parasite free through June 1978.

TABLE 1  
Laboratory studies performed to detect a potential cause of diarrhea and eosinophilia other than *Entamoeba polecki*. All had normal results

|   |
|---|
| Serology*   |
| Amebic IHA (× 4)  |
| Schistosomal CFT and IFA                                      |
| <i>Trichinella</i> LA slide test                              |
| Filarial BFT and IHA  |
| Procedures  |
| Sigmoidoscopy (× 2)   |
| Rectal biopsy (histological and press exams)                  |
| Barium enema  |
| Gall bladder series   |
| Duodenoscopy and small intestinal biopsy                      |
| Duodenal aspirate examination                                 |
| Upper gastrointestinal series with small bowel follow through |

\* IHA, indirect hemagglutination test; CFT, complement-fixation test; IFA, indirect fluorescent antibody test; LA, latex agglutination; BFT, bentonite flocculation test.

Differentiation between cysts of *E. histolytica*, *E. polecki*, and *E. coli* can be difficult.<sup>1,7</sup> There are five major points of distinction between *E. histolytica* and *E. polecki*, the two amebae most often confused. First, *E. polecki* has a single nucleus with only about 1% of cysts reaching a binucleate stage. *E. histolytica* is infrequently uninucleate, and usually more mature cysts are seen containing 2-4 nuclei. The presence of only single nuclear forms in the stool should raise the suspicion of *E. polecki*. Second, the nucleus in the cyst of *E. polecki* is usually one-fourth to one-third the cyst's diameter and contains a large karyosome with variations of the chromatin pattern. In contrast, the *E. histolytica* nucleus is larger, being one-third to one-half the cyst's diameter, with a small karyosome and uniform distribution of peripheral nuclear chromatin. Third, *E. polecki* cysts rarely have glycogen vacuoles which are commonly seen with *E. histolytica*. However, an inclusion mass—a darkly stained body 3-4 times the size of the nucleus—is often found in the cytoplasm of *E. polecki*. It is not found in *E. histolytica*. Fourth, *E. histolytica* usually contains less than ten chromatin bars; *E. polecki* may have as many as thirty. Finally, *E. histolytica* is readily treatable; whereas, *E. polecki* is virtually refractory to therapy.<sup>3</sup> *E. polecki* is not invasive beyond the intestine; whereas, *E. histolytica* is well known for extra-intestinal complications.

This is only the second recorded case of symptomatic illness secondary to *E. polecki* intestinal infection. Levin and Armstrong reported a 21-year-old female Peace Corps volunteer stationed in India with documented infestation for 18 months, the last 7 months away from the presumed contact area in India.<sup>1</sup> Our patient persisted in having uncontrolled symptomatic *E. polecki* intestinal disease for 10 months after leaving Africa until he was finally successfully treated. Furthermore, his diarrhea during the 9 years in Africa could have been at least in part due to *E. polecki* infection.

This infection has never previously been successfully eradicated from a human host. After 9 months of follow-up, with 12 negative stool examinations, we consider the patient's infection to be cured. To our knowledge, this is the first time that diloxanide furoate had been used specifically to treat *E. polecki* infection. It is used as a luminal amebicide, and when combined with metronidazole is considered an ideal regimen for acute amebic dysentery.<sup>9,10</sup> Side effects are virtually nonexistent with the exception of increased flatulence. It is also useful to eliminate cyst carriers and as an adjunct to metronidazole in treating amebic liver abscesses.<sup>11</sup> It is not known whether diloxanide furoate alone is sufficient to cure *E. polecki* infections. A combination with metronidazole, as used to treat our patient, may be required.

We found no explanation for this patient's persistent eosinophilia. Blood smears and serological tests for both filariae and trichinosis were negative, as were repeated stool examinations for other intestinal parasites and a duodenal aspirate looking for *Strongyloides stercoralis*. There was no clinical or laboratory evidence for a collagen vascular disease, allergies or leukemia.

#### ACKNOWLEDGMENT

Dr. Martin Wolfe of the Department of Parasitology supplied the diloxanide furoate and reviewed the manuscript.

#### REFERENCES

1. Levin, R. L., and Armstrong, D. E., 1970. Human infections with *Entamoeba polecki*. *J. Clin. Pathol.*, 54: 611-614.

2. von Prowazek, S., 1912. *Entamoeba*. *Arch. Protistenk.*, 25: 273-274.
3. Kessel, J. F., and Johnstone, H. G., 1949. The occurrence of *Entamoeba polecki*, Prowazek 1912, in *Macaca mulatta* and man. *Am. J. Trop. Med.*, 29: 311-317.
4. Lawless, D. K., 1954. Report on a human case of *Entamoeba polecki*, Prowazek, 1912. *J. Parasitol.*, 40: 221-228.
5. Burrows, R. B., and Klink, G. E., 1955. *Entamoeba polecki* infections in man. *Am. J. Hyg.*, 62: 156-167.
6. Lawless, D. K., and Knight, V., 1966. Human infection with *Entamoeba polecki*: Report of four cases. *Am. J. Trop. Med. Hyg.*, 15: 701-704.
7. Burrows, R. B., 1959. Morphological differentiation of *Entamoeba hartmanni* and *E. polecki* from *E. histolytica*. *Am. J. Trop. Med. Hyg.*, 8: 583-589.
8. Kessel, J. F., and Kaplan, F., 1949. The effect of certain arsenicals on natural infections of *Entamoeba histolytica* and of *Entamoeba polecki* in *Macaca mulatta*. *Am. J. Trop. Med.*, 29: 319-322.
9. Wolfe, M., 1973. Nondysenteric intestinal amoebiasis. Treatment with diloxamide furate. *J. Am. Med. Assoc.*, 224: 1601-1604.
10. Dubey, M. P., Gupta, P. S., and Chuttani, H. K., 1965. Entamide furate in the treatment of intestinal amoebiasis. *J. Trop. Med. Hyg.*, 68: 63-66.
11. Powell, S. J., Stewart-Wynne, E. J., and Elsdon-Dew, R., 1973. Metronidazole combined with diloxamide furate in amoebic liver abscesses. *Ann. Trop. Med. Parasitol.*, 67: 367-368.

## SUCCESSFUL TREATMENT OF SYMPTOMATIC *ENTAMOEBA POLECKI* INFECTION\*

J. S. SALAKI, J. L. SHIREY, AND G. T. STRICKLAND

Department of Medicine, National Naval Medical Center and Uniformed Services  
University of the Health Sciences, Bethesda, Maryland 20014

**Abstract.** The second symptomatic case of *Entamoeba polecki* infection, the first to respond to therapy, is reported. The patient experienced intermittent episodes of abdominal cramps, diarrhea, nausea, and malaise associated with large numbers of *E. polecki* cysts in the stool. Following treatment with diloxanide furoate and metronidazole, all symptoms cleared and the parasite was no longer present in the stool.

Human infection with *Entamoeba polecki* is rare and the parasite has been confused microscopically with *Entamoeba histolytica*.<sup>1</sup> It is generally considered not to be a pathogen for man. Herein, we report a case of prolonged symptomatic *E. polecki* intestinal disease in a patient in whom medical treatment for the organism resulted in the first clinical and laboratory cure. This is the 20th human case reported, the second in which the patient had been symptomatic.

### CASE REPORT

D. McK., a 24-year-old Peace Corps volunteer, had been stationed in Upper Volta between July 1974 and June 1976, living in the back-country in open huts into which local domestic animals would freely roam. Pertinent animal contact occurred with pigs as well as with a pet monkey. Before entering the Peace Corps, he had no prior history of gastrointestinal disease. However, while in Africa, he experienced multiple episodes of dysentery diagnosed as both amebic and bacillary. With each episode he was treated with appropriate therapy and obtained temporary symptomatic improvement.

When discharged from the Peace Corps in June 1976 he again experienced abdominal pain and diarrhea and was successfully treated for hook-

worm infection. Nevertheless, he continued to have mucoid stools, diarrhea, nausea, headache, weakness, malaise, and abdominal cramps. His weight, which had been 155 lbs in June 1974, was 134 lbs 2 years later.

In September 1976 the patient was first seen at the National Naval Medical Center for investigation of his continued gastrointestinal complaints. At that time his physical examination was unremarkable, other than mucoid stool on rectal exam. A stool specimen observed for parasites showed a heavy infection with *Entamoeba polecki* and he had a 26% eosinophilia (Fig. 1).

The patient was begun on a course of metronidazole, 750 mg three times per day for 10 days and diiodohydroxyquin, 650 mg three times per day for 20 days. Although subjective improvement occurred and the parasite was absent from the stool briefly, both *E. polecki* cysts and his symptoms recurred (Fig. 2). Over the next 10 months the patient received numerous courses of treatment with anti-amebicides, with no sustained resolution of either symptoms or presence of the organism in his stool specimens, although symptomatic improvement often coincided with reductions in numbers of cysts in the feces during therapy. Extensive laboratory investigations seeking another cause of his diarrhea and eosinophilia were normal or negative and are listed in Table 1. All routine laboratory tests were normal. A total of 31 stool specimens were examined with no other intestinal parasites observed. *Schistosoma haematobium* were not present in the urine. Repeated thick blood films did not show filariae. However, eosinophilia was always present although it diminished after successful therapy for the *E. polecki*, it persisted (Figs. 1 and 2).

In July 1977, the luminal agent, diloxanide

Accepted 13 September 1978.

\* The opinions or assertions contained herein are the private ones of the authors and not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

Address reprint requests to: CAPT. G. T. Strickland, MC, USN, Department of Medicine, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, Maryland 20014.

NOTICE  
THIS MATERIAL MAY BE PROTECTED BY  
COPYRIGHT LAW (TITLE 17, U.S. CODE)

Reprinted with permission  
through the Copyright  
Clearance Center

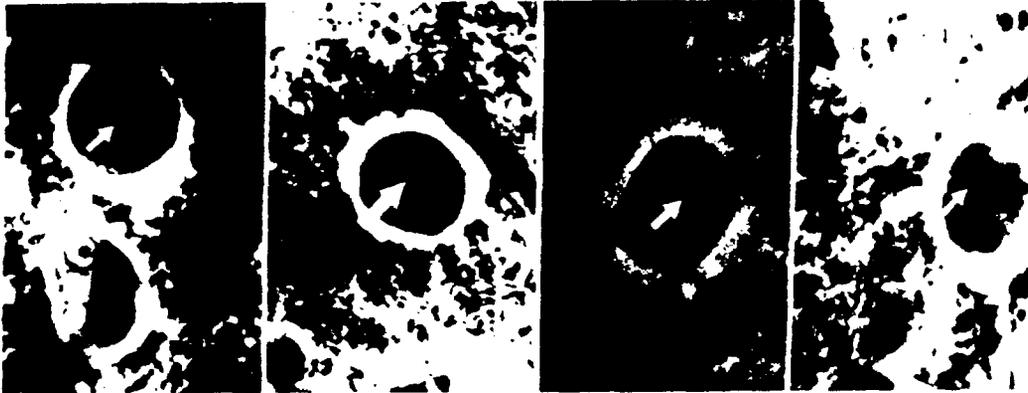


FIGURE 1. Representative *E. polecki* cysts. The karyosome is large in comparison with the nucleus and chromatin is abundant in the nuclear membrane. Chromatoid bodies are numerous (long arrow) while inclusion masses (short arrows) are seen in some cysts. Lawless and trichrome stain,  $\times 960$ .

furoate (Furamide®), was used for the first time. Following a 10-day course of metronidazole 750 mg three times per day, diloxanide furoate was given for 10 days, 500 mg three times daily. Upon completion of taking both agents, he noticed subjective improvement in his condition with resolution of abdominal cramps, more formed, less mucoid stools and improved appetite. Although he had a rare isolated stool negative for parasites associated with treatment in the prior 10 months, he has subsequently had 12 consecutive negative stool exams over the past 12 months and only rarely has a loose stool following a dietary indiscretion, e.g., excessive beer consumption.

DISCUSSION

*Entamoeba polecki* was first described and named by von Prowazek in 1912 when it was first seen by him in pigs and later monkeys, cattle, and sheep, and was named after Dr. Poleck, a Samoan physician.<sup>2</sup> The life cycle includes both trophozoite and cyst stages, although trophozoites are infrequently seen in the stool. Almost exclusively described as a parasite of pigs and monkeys, it has been found in human stools on rare occasions.<sup>1,3-6</sup> Transmission from certain domestic animals, particularly pigs and monkeys, is the most likely source of infection, but human-to-human spread has also been suggested.<sup>6</sup>

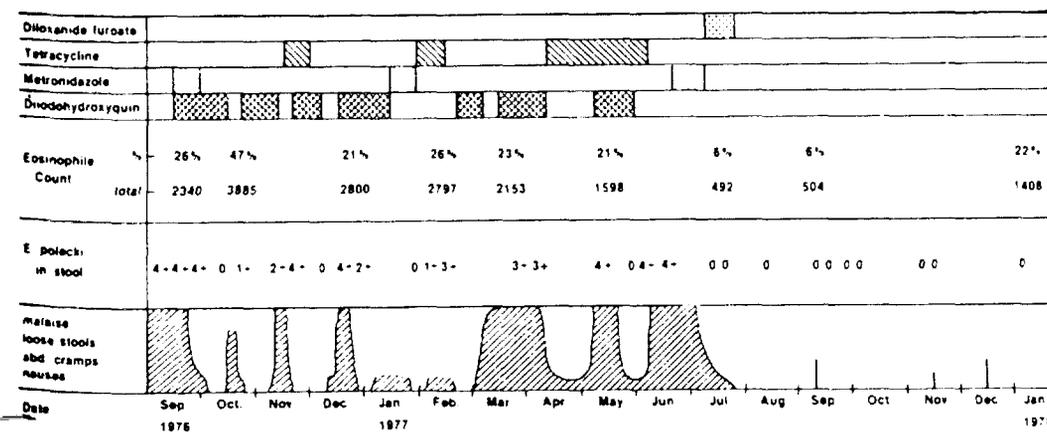


FIGURE 2. Course of illness showing symptoms, *E. polecki* cysts in stools, eosinophil count, and treatment. The patient remains asymptomatic and parasite free through June 1978.

TABLE 1  
Laboratory studies performed to detect a potential cause of diarrhea and eosinophilia other than *Entamoeba polecki*. All had normal results

|   |
|---|
| Serology*   |
| Amebic IHA (× 4)  |
| Schistosomal CFT and IFA                                      |
| <i>Trichinella</i> LA slide test                              |
| Filarial BFT and IHA  |
| Procedures  |
| Sigmoidoscopy (× 2)   |
| Rectal biopsy (histological and press exams)                  |
| Barium enema  |
| Gall bladder series   |
| Duodenoscopy and small intestinal biopsy                      |
| Duodenal aspirate examination                                 |
| Upper gastrointestinal series with small bowel follow through |

\* IHA, indirect hemagglutination test; CFT, complement-fixation test; IFA, indirect fluorescent antibody test; LA, latex agglutination; BFT, bentonite flocculation test.

Differentiation between cysts of *E. histolytica*, *E. polecki*, and *E. coli* can be difficult.<sup>1,7</sup> There are five major points of distinction between *E. histolytica* and *E. polecki*, the two amebae most often confused. First, *E. polecki* has a single nucleus with only about 1% of cysts reaching a binucleate stage. *E. histolytica* is infrequently uninucleate, and usually more mature cysts are seen containing 2-4 nuclei. The presence of only single nuclear forms in the stool should raise the suspicion of *E. polecki*. Second, the nucleus in the cyst of *E. polecki* is usually one-fourth to one-third the cyst's diameter and contains a large karyosome with variations of the chromatin pattern. In contrast, the *E. histolytica* nucleus is larger, being one-third to one-half the cyst's diameter, with a small karyosome and uniform distribution of peripheral nuclear chromatin. Third, *E. polecki* cysts rarely have glycogen vacuoles which are commonly seen with *E. histolytica*. However, an inclusion mass—a darkly stained body 3-4 times the size of the nucleus—is often found in the cytoplasm of *E. polecki*. It is not found in *E. histolytica*. Fourth, *E. histolytica* usually contains less than ten chromatin bars; *E. polecki* may have as many as thirty. Finally, *E. histolytica* is readily treatable; whereas, *E. polecki* is virtually refractory to therapy.<sup>8</sup> *E. polecki* is not invasive beyond the intestine; whereas, *E. histolytica* is well known for extra-intestinal complications.

This is only the second recorded case of symptomatic illness secondary to *E. polecki* infection. Levin and Armstrong reported a 1-year-old female Peace Corps volunteer stationed in India with documented infestation for 18 months, the last 7 months away from the presumed contact area in India.<sup>1</sup> Our patient persisted in having uncontrolled symptomatic *E. polecki* intestinal disease for 10 months leaving Africa until he was finally successfully treated. Furthermore, his diarrhea during 10 years in Africa could have been at least in part due to *E. polecki* infection.

This infection has never previously been successfully eradicated from a human host. After 9 months of follow-up, with 12 negative stool examinations, we consider the patient's infection to be cured. To our knowledge, this is the first time that diloxanide furoate had been used specifically to treat *E. polecki* infection. Diloxanide furoate is used as a luminal amebicide, and when combined with metronidazole is considered an ideal regimen for acute amebic dysentery.<sup>9,10</sup> Side effects are virtually nonexistent with the exception of increased flatulence. It is also useful to eliminate cyst carriers and as an adjunct to metronidazole in treating amebic liver abscesses.<sup>11</sup> It is not known whether diloxanide furoate alone is sufficient to cure *E. polecki* infections. A combination with metronidazole, as used to treat our patient, may be required.

We found no explanation for this patient's persistent eosinophilia. Blood smears and serological tests for both filariae and trichinosis were negative, as were repeated stool examinations for other intestinal parasites and a duodenal aspirate looking for *Strongyloides stercoralis*. There is no clinical or laboratory evidence for a collagen vascular disease, allergies or leukemia.

#### ACKNOWLEDGMENT

Dr. Martin Wolfe of the Department of Pathology supplied the diloxanide furoate and reviewed the manuscript.

#### REFERENCES

- Levin, R. L., and Armstrong, D. E., 1970. Human infections with *Entamoeba polecki*. *J. Clin. Pathol.*, 54: 611-614.

2. von Prowazek, S., 1912. *Entamoeba*. *Arch. Protistenk.*, 25: 273-274.
3. Kessel, J. F., and Johnstone, H. G., 1949. The occurrence of *Endamoeba polecki*, Prowazek 1912, in *Macaca mulatta* and man. *Am. J. Trop. Med.*, 29: 311-317.
4. Lawless, D. K., 1954. Report on a human case of *Endamoeba polecki*, Prowazek, 1912. *J. Parasitol.*, 40: 221-228.
5. Burrows, R. B., and Klink, G. E., 1955. *Endamoeba polecki* infections in man. *Am. J. Hyg.*, 62: 156-167.
6. Lawless, D. K., and Knight, V., 1966. Human infection with *Entamoeba polecki*: Report of four cases. *Am. J. Trop. Med. Hyg.*, 15: 701-704.
7. Burrows, R. B., 1959. Morphological differentiation of *Entamoeba hartmanni* and *E. polecki* from *E. histolytica*. *Am. J. Trop. Med. Hyg.*, 8: 583-589.
8. Kessel, J. F., and Kaplan, F., 1949. The effect of certain arsenicals on natural infections of *Endamoeba histolytica* and of *Endamoeba polecki* in *Macaca mulatta*. *Am. J. Trop. Med.*, 29: 319-322.
9. Wolfe, M., 1973. Nondysenteric intestinal amoebiasis. Treatment with diloxamide furate. *J. Am. Med. Assoc.*, 224: 1601-1604.
10. Dubey, M. P., Gupta, P. S., and Chuttani, H. K., 1965. Entamide furate in the treatment of intestinal amoebiasis. *J. Trop. Med. Hyg.*, 68: 63-65.
11. Powell, S. J., Stewart-Wynne, E. J., and Elsdon-Dew, R., 1973. Metronidazole combined with diloxamide furate in amoebic liver abscesses. *Ann. Trop. Med. Parasitol.*, 67: 367-368.

# Nondysenteric Intestinal Amebiasis

## Treatment With Diloxanide Furoate

NOTICE

THIS MATERIAL MAY BE PROTECTED BY  
COPYRIGHT LAW (TITLE 17, U.S. CODE)

Martin S. Wolfe, MD

Diloxanide furoate, an investigational, amebicidal drug in the United States, was given in a ten-day course of 500 mg three times a day. This therapy led to parasitologic and symptomatic cure in all 12 asymptomatic cyst carriers and in 52 of 65 patients with nondysenteric, symptomatic, intestinal amebiasis who had all contracted *Entamoeba histolytica* infections while abroad. Criteria for cure were the absence of *E histolytica* parasites in three complete stool examinations, one and three months following completion of treatment, and complete or marked symptomatic improvement. Excessive flatulence was a common, but the only significant side effect. The high effectiveness (83% cure rate), relative ease of administration, and minimal toxicity of diloxanide furoate indicates that this drug has numerous advantages over other primarily luminal-acting amebicides presently available in this country for the treatment of chronic amebiasis.

More than 90% of the individuals seen in our Tropical Medicine Unit, who have contracted amebiasis while traveling or living abroad, had an asymptomatic or a nondysenteric chronic or subacute form of infection. Similar findings are also reported in returnees to England and France.<sup>1,2</sup> It is much more unusual in these countries to see the fulminant dysenteric form of amebiasis in travelers, with its typical presentation of frequent bloody stools, fever, marked abdominal cramps, tenesmus, and weight loss. A spectrum of symptoms is seen with nondysenteric *Entamoeba histolytica* infections, ranging from asymptomatic and mildly symptomatic individuals with complaints of increased number of soft stools, intermittent constipation, excessive distention and flatulence, and increased fatigue to more severely infected individuals who do not have frank amebic dysentery, but show evidence of some invasion of the bowel wall as manifested by very frequent watery to mushy

stools, lower abdominal cramps, weight loss, anorexia and nausea, and marked asthenia. The asymptomatic and mildly symptomatic individuals fit most definitions of so-called chronic amebiasis, while the more severely affected individuals could be said to have a subacute type of infection. The present report concerns 100 individuals exposed to amebiasis while living or traveling outside the United States and found, upon their return to Washington, DC, to have cysts larger than 10 $\mu$ , or trophozoites fitting the definition for *E histolytica*. These people were treated with diloxanide furoate (Furamide).

A number of anilides looked promising as amebicides and one of them, dichloroacet-4-hydroxy-N-methylanilide, was selected for further investigation. Ultimately, after extensive laboratory and clinical investigations, it was marketed in Britain under the name of Entamide and received the approved name diloxanide. Further investigations were carried out to find a derivative of diloxanide which would give better results in acute as well as in chronic amebiasis. Of the many derivatives examined, the furoate ester not only gave better results in acute amebic dysentery, but in the asymptomatic condition as well; it also was less toxic than diloxanide itself. This compound was given the name diloxanide furoate. It is less

soluble than its earlier parent compound and is more slowly absorbed from the bowel and excreted from the body, thus providing a higher concentration in the bowel wall and lumen for a longer period of time. Diloxanide furoate has been used extensively outside of the United States for more than 15 years in the treatment of amebiasis, but has not been licensed in this country and is restricted by federal law to investigational use. Early studies carried out in various parts of the world with diloxamide furoate used by itself, both in indigenous populations in highly endemic amebiasis areas, and to a lesser extent in returnees from amebiasis-endemic areas to England and France, have claimed cure rates of more than 90% in the chronic forms of amebiasis and cure rates in the range of 80% in the treatment of acute amebic dysentery.<sup>1,3</sup> However, diloxanide furoate gave only a 40% cure rate and was considered inadequate treatment for acute amebic dysentery encountered in Durban, South Africa.<sup>4</sup> Other workers also consider diloxanide furoate inferior to other better-absorbed drugs in acute amebic dysentery where there is significant tissue invasion.<sup>5,6</sup>

The only previous studies of diloxanide furoate in the United States were by McHardy in 1960 who reported a 90% cure rate in asymptomatic amebiasis patients (Panel on Diarrheal Disease, clinical meeting of the American Medical Association, Washington, DC); and Most (written communication, March 1970), who used diloxanide furoate both with and without chloroquine phosphate and had cure rates between 75% and 80%. Neither of these investigators reported significant toxicity.

With its reported high effectiveness, relative ease of administration, and minimal toxic effects, diloxanide furoate appeared to have numerous advantages over other primarily luminal-acting amebicides presently available in the United

From the Tropical Medicine Unit, Office of Medical Services, Department of State, Washington, DC.

Read in part before the 20th annual meeting of the American Society of Tropical Medicine and Hygiene, Boston, Dec 3, 1971.

Reprint requests to Office of Medical Services, Department of State, Washington, DC 20520 (Dr. Wolfe).

| Follow-Up               | No. Treated | Cured†    |           |
|-------------------------|-------------|-----------|-----------|
|                         |             | No.       | %         |
| Complete                |             |           |           |
| Asymptomatic cases      | 12          | 12        | 100       |
| Symptomatic cases       | 65          | 52        | 80        |
| <b>Total</b>            | <b>77</b>   | <b>64</b> | <b>83</b> |
| Incomplete (eliminated) |             |           |           |
| Asymptomatic cases      | 6           | ...       | ...       |
| Symptomatic cases       | 17          | ...       | ...       |
| <b>Total</b>            | <b>23</b>   |           |           |
| <b>Grand total</b>      | <b>100</b>  |           |           |

\*One hundred cases treated with diloxanide furoate.

†Based on three negative results from complete stool examinations at one and three months after treatment (a total of six negative stools) and a complete or marked symptomatic improvement.

| Symptom                            | Pretreatment |               | Posttreatment |               |
|------------------------------------|--------------|---------------|---------------|---------------|
|                                    | Cured (52)   | Failure† (13) | Cured (52)    | Failure† (13) |
| Anorexia                           | 7            | 2             | 0             | 0             |
| Nausea                             | 6            | 2             | 0             | 0             |
| Weight loss                        | 10           | 1             | 0             | 0             |
| Mushy stools                       | 40           | 8             | 11            | 4             |
| Watery stools                      | 1            | 1             | 0             | 0             |
| Mucus                              | 4            | 1             | 0             | 0             |
| Intermittent constipation          | 11           | 2             | 0             | 2             |
| Abdominal cramps                   | 12           | 3             | 3             | 0             |
| Distention                         | 16           | 5             | 1             | 2             |
| Flatulence                         | 31           | 8             | 5             | 4             |
| Fatigue                            | 17           | 5             | 3             | 1             |
| At least one posttreatment symptom |              |               | 17            | 8             |

\*Sixty-five symptomatic cases with complete follow-up. Twelve asymptomatic cases not included.

†Based on the persistence of *E histolytica* parasites in posttreatment stool specimens.

States for the treatment of non-dysenteric forms of amebiasis. A new drug investigation application was filed with the Food and Drug Administration for diloxanide furoate, and the study to be described was carried out from June 1970 through December 1971.

### Materials and Methods

The 100 individuals in the study included 84 US foreign service employees or their dependents; all but five of these were adults, a reflection of the primarily adult population seen in the Tropical Medicine Unit of the Department of State Office of Medical Services. A further 16 adults were employees of the World Bank Group, comprising various nationalities, who reside in Washington, DC, but make frequent short trips to countries in the developing world. Eighteen patients were asymptomatic and the remaining 82 had mild to moderate symptoms from their infection.

Criteria for inclusion in the study included the finding of *E histolytica*

cysts or trophozoites or both in at least one pretreatment stool examination; the absence of severe symptoms or proctoscopic findings compatible with acute amebic dysentery; and an expectation that the patient would remain in Washington, DC, during the three-month follow-up period. However, the nature of the patients' work required sudden travel to amebiasis endemic areas during this follow-up period in some cases. Informed consent for use of an investigational drug was obtained from all patients. Pretreatment and posttreatment proctoscopic examinations were not routinely carried out.

The criterion for parasitologic cure was the absence of *E histolytica* parasites in three stool examinations carried out one and three months following the completion of treatment, for a total of six negative specimens. All stool examinations were performed by the parasitology laboratory of the Department of State Office of Medical Services. Each examination consisted of direct smears in saline and

iodine, zinc sulfate, and formaldehyde-ether concentration, and an aerobic culture utilizing liver-cholesterol broth. Dobell's hematoxylin-stained slides were made from any specimen containing suspicious parasites. In some cases, when patients had been suddenly reassigned or were abroad at the time of follow-up, specimens were sent to our laboratory for thimerosal-iodine-formaldehyde preservation, and direct smear and concentration technique were performed on these specimens. Complete or marked symptomatic improvement was also necessary to consider an individual to be cured.

All subjects were treated on an outpatient basis. Adults were given a course of 500 mg of diloxanide furoate three times daily for ten days and children were given 20 mg/kg body weight daily in three divided doses for ten days.

Pretreatment and immediate posttreatment white blood cell count, hematocrit reading, and urine albumin and sediment examinations were performed by the clinical laboratory of the Department of State Office of Medical Services. Following the completion of the treatment course, patients were questioned as to the occurrence of side effects and improvement in symptoms.

### Results

Twenty-three patients did not have satisfactory results of posttreatment follow-up stool examinations and were eliminated from the study. Six of these were asymptomatic and the other 17 were symptomatic.

All 12 of the asymptomatic patients who had complete follow-up had six negative results for stool examinations and were considered parasitologically cured.

Sixty-five symptomatic patients had complete follow-up and 52 of these were considered parasitologically cured and symptomatically improved, a cure rate of 80% in the group (Table 1). Of the 13 parasitologic failures, five had complete symptomatic improvement, while at least one pretreatment symptom persisted in the remaining eight. Nine of the 13 treatment failures were manifested at the one-month follow-up examination and two of those four

positive at the three-month follow-up examination had traveled to amebiasis-endemic areas between the one- and three-month follow-up examinations. Six patients with treatment failure were given a second course of diloxanide furoate and three were cured, but *E histolytica* infection persisted in the other three. These second courses of diloxanide furoate are not included in determining cure rates.

The total cure rate obtained in the 77 patients (12 asymptomatic and 65 symptomatic) with satisfactory follow-up findings was 83% (Table 1).

In the successfully treated symptomatic group, all those with symptoms of anorexia, nausea, constipation, and weight loss, were free from these symptoms following treatment. Eleven individuals with soft stools before treatment continued to have soft stools during follow-up. Five of the 31 individuals who had had excessive flatulence still had this complaint after treatment, but only one of 16 individuals who had complained of distention continued to have this disturbance. Fatigue persisted in only one of 17 people who had had this complaint (Table 2).

Twenty-six patients who had complete follow-up had coincidental *Entamoeba hartmanni* infections before treatment, and in only two of them was this parasite present in post-treatment specimens.

A universal side effect was excessive flatulence, and 87% of those questioned as to occurrence of side effects complained of this. The only other significant side effects occurred in five patients who complained of nausea, three of anorexia, two of diarrhea, and two of mild abdominal cramps while taking the drug, but all completed the full course of treatment without incident (Table 3). No significant abnormalities were found between pretreatment and post-treatment blood cell counts and urinalyses.

### Comment

The results of this investigation, the elimination of cysts from all 12 asymptomatic patients, and an overall cure rate of 83% in the 77 diloxanide furoate-treated patients with adequate follow-up, are similar to those of the two previous studies of

Table 3.—Side Effects\*

|                         | Recorded | %    |
|-------------------------|----------|------|
| Flatulence              | 78       | 87.4 |
| Anorexia                | 3        | 3.3  |
| Nausea                  | 5        | 5.6  |
| Diarrhea                | 2        | 2.2  |
| Abdominal cramps (mild) | 2        | 2.2  |

\*One hundred patients treated with diloxanide furoate. Ninety were followed up and recorded and ten were in a group with no or an incomplete follow-up.

this drug in the United States by McHardy and Most (written communication, March 1970). The results are also considered comparable to those obtained in other investigations of diloxanide furoate in nonendemic amebiasis areas. In one of the early studies of diloxanide furoate at the Hospital for Tropical Diseases in London, a 95.5% cure rate was obtained in 35 patients with chronic amebiasis when given a standard ten-day course of diloxanide furoate. However, in that study the mean number of follow-up stool examinations was only 1.5; and it is quite likely that if six follow-up examinations over a three-month period had been carried out as in the present study, the cure rate would have dropped somewhat. In another study, Felix et al<sup>7</sup> treated 54 young adults with chronic amebiasis, who had returned to France after having spent a period in Algeria, with a standard course of diloxanide furoate. Cure was claimed for all but two of these patients, but follow-up, for the most part, was accomplished for only a fortnight after the end of treatment.<sup>7</sup> Other reported trials showing a high cure rate with diloxanide furoate were carried out primarily on residents in highly endemic amebiasis areas,<sup>8</sup> and are not thought to be comparable to the present trial that was carried out in nonendemic areas where the disease manifestations differ and the risk of reinfection during follow-up is minimal.

The good result with only minor attendant side effects obtained in this study with a ten-day course of diloxanide furoate compares favorably with and in many respects is superior to other amebicides used in the United States and elsewhere in the treatment of nondysenteric amebiasis. In England, orally given emetine-bismuth-iodide is suggested as the standard of reference against other amebicides in drug trials,<sup>9</sup> but this

drug is not available in the United States and frequent troublesome side effects can occur with its use. Tetracyclines, particularly oxytetracycline (Terramycin), and tetracycline hydrochloride, usually given in a dose of 1 or 2 gm daily for ten days, are highly effective in acute amebic dysentery, but relapse rates are high.<sup>10</sup> However, when this course is combined with or followed by a 21-day course of 650 mg of diiodohydroxyquin (Diodoquin) three times a day (often this course is combined or followed with a four-week course of chloroquine phosphate to prevent later development of liver abscess), cure rates as high as 95% without relapse have been obtained in acute amebic dysentery.<sup>10</sup> There are no valid reports on the effectiveness of this combined regimen in the more chronic forms of amebiasis, but cure rates of 80% to 90% should be obtainable. However, this regimen has numerous drawbacks, including (1) a prolonged course of treatment, (2) the not infrequent occurrence of diarrhea, (3) the potential risk of bacterial and monilial overgrowth, (4) teeth discoloration in children due to the tetracycline; and (5) the potential for reactions to iodine with diiodohydroxyquin. Diiodohydroxyquin, by itself in a 21-day course, is usually well tolerated and provides cures on the order of at least 75% in chronic amebiasis,<sup>10</sup> but again there is a rather prolonged course of treatment and iodine-sensitive individuals cannot use it. Also, this drug, though to a far lesser degree than the related compound iodochlorhydroxyquin (Entero-Vioform),<sup>11</sup> has led to a few cases of optic atrophy or polyneuropathy or both with long-term administration of larger doses than recommended for treatment of amebiasis, such as in the management of acrodermatitis enteropathica.<sup>12</sup> Paromomycin (Humatin) can be given in a short course and cure rates averaging 80% have been reported, but it is more effective in acute intestinal amebiasis than in the asymptomatic carrier state.<sup>13</sup> When it is used alone, relapses are frequent, and in the required doses, it frequently causes diarrhea and other gastrointestinal complaints and can lead to a reversible malabsorption defect.<sup>14</sup> Carbarsone, an arsenical, when employed alone is curative in only

about 50% of cases.<sup>6</sup> Although it is normally well tolerated, fatalities as a result of exfoliative dermatitis, liver necrosis, or hemorrhagic encephalitis have been reported.<sup>15</sup> Glycobiarsol (Milibis), is also an arsenical and when given alone, the cure rate is disappointingly low.<sup>16</sup> Although side effects are fewer with glycobiarsol than with carbarsone, isolated instances of arsenical toxicity have been reported.<sup>16</sup> In view of the wide range of amebicides available, it is doubtful whether arsenicals should be used for a chronic condition. Metronidazole has been heralded as the most effective drug for all forms of amebiasis. Although metronidazole has been shown to be highly effective in acute invasive forms of amebiasis,<sup>17</sup> claims that it is superior to primarily luminal-acting drugs, when used by itself in noninvasive forms of amebiasis, are not substantiated in all studies. Quite favorable results were obtained by the use of metronidazole alone in various dosage regimens in Pakistan<sup>18</sup> and India.<sup>19</sup> But studies in Bangkok<sup>20</sup> and London<sup>21</sup> showed metronidazole by itself to be much less satisfactory for the treatment of noninvasive forms of amebiasis in the lumen of the bowel. In the London study, carried out at the Hospital for Tropical Diseases, it was concluded that the cure rate in these forms of amebiasis was no higher with metronidazole in adequate doses than with diloxanide furoate alone, and side effects were more common and troublesome. It was thought that metronidazole is less effective as a luminal amebicide because it is almost completely absorbed from the small bowel and may thus only affect intraluminal amebae if they are in very close proximity to the colonic mucosa.<sup>21</sup>

A two- to four-week course of chloroquine phosphate, concomitant with or following the use of some of the drugs discussed, is often employed as a precautionary measure against the possible subsequent occurrence of amebic liver abscess.<sup>22</sup> The later development of amebic liver abscess is a rare occurrence in well-nourished, otherwise healthy individuals with nondysenteric amebiasis who comprised the subjects of the present study. Since side effects of chloroquine phosphate are frequent

and may be additive to those caused by primary bowel-active drugs, such as diloxanide furoate (or tetracyclines, metronidazole, or diiodohydroxyquin used in other studies), and since we have not encountered amebic liver abscess following the use of these drugs, chloroquine phosphate has not been used as a routine precautionary measure in the treatment of the usual noninvasive amebiasis patient in our unit.

Little is known concerning possible teratogenic effects of diloxanide furoate, and since the main indication for its use is for a nonacute condition, it appears best at this time to withhold its use at least during the early stage of pregnancy. Some investigators have shown activated charcoal to be beneficial in decreasing the only common side effect of diloxanide furoate, excessive flatulence,<sup>2</sup> but this preparation was not used in the present study.

Although diloxanide furoate by itself may not be a satisfactory treatment for acute amebic dysentery,<sup>1,2</sup> it holds great promise as a luminal amebicide in a follow-up course of treatment to metronidazole in cases of acute amebiasis, particularly if diloxanide furoate becomes licensed and readily available for treatment of amebiasis in this country. This combination of metronidazole (in a dose of 500 to 750 mg three times a day for five to ten days) followed by a ten-day standard course of diloxanide furoate, could possibly represent a near ideal regimen for acute amebic dysentery and could also possibly lead to an even higher cure rate in nondysenteric amebiasis than either drug alone. It might also prove superior to the present commonly used regimen of a course of metronidazole followed by 21 days of diiodohydroxyquin therapy, which was recently reported to have been followed by the appearance of amebic liver abscesses in five patients whose amebic colitis had been successfully treated with these two drugs.<sup>23</sup> We are presently evaluating a regimen of metronidazole and diloxanide furoate in a series of patients with more acute signs and symptoms of amebiasis than those included in the present investigation, wherein diloxanide furoate by itself has been shown to be an effective, safe, and simple regimen for the

treatment of chronic and subacute nondysenteric amebiasis.

Diloxanide furoate would therefore appear to be a valuable addition to the assortment of amebicidal drugs used in this country and it is hoped that it can be soon licensed for routine use.

#### Nonproprietary Name and Trademark of Drug

Metronidazole—Flagyl.

#### References

1. Woodruff AW, Bell S: The evaluation of amebicides. *Trans R Soc Trop Med Hyg* 61:435-439, 1967.
2. Felix H, et al: Treatment of amoebiasis with entamide furoate. *Bull Soc Pathol Exot* 55:370-379, 1962.
3. Botero D: Treatment of acute and chronic intestinal amebiasis with entamide furoate. *Trans R Soc Trop Med Hyg* 58:419-421, 1964.
4. Wilmot AJ, et al: Some newer amebicides in acute amebic dysentery. *Trans R Soc Trop Med Hyg* 56:85-86, 1962.
5. Seaton DR: Amebicides. *Gut* 206:16-19, 1971.
6. Marsden PD, Schultz MG: Intestinal parasites. *Gastroenterology* 57:724-750, 1969.
7. Sapero JJ, Lawless DK: The "MIF" stain-preservation technique for the identification of intestinal protozoa. *Am J Trop Med Hyg* 2:613-619, 1953.
8. Woodruff AW, Bell S: Clinical trials with entamide furoate and related compounds: I. In a non-tropical environment. *Trans R Soc Trop Med Hyg* 54:389-395, 1960.
9. Powell SJ: Short-term followup studies in amebic dysentery. *Trans R Soc Trop Med Hyg* 61:765-768, 1967.
10. Most H: Current concepts in therapy. Treatment of amebiasis. *N Engl J Med* 262:513-514, 1960.
11. Schultz MG: Entero-Vioform for preventing travelers' diarrhea, editorial. *JAMA* 220:273-274, 1972.
12. Annotations: Clotrimazole and other halogenated hydroxyquinolines. *Lancet* 1:679, 1968.
13. Sodeman WA Jr: Amebiasis (clinical seminar). *Am J Dig Dis* 16:51-60, 1971.
14. Keusch GT, et al: Malabsorption due to paromomycin. *Arch Intern Med* 125:273-276, 1970.
15. Radke RA, Baroody WG: Carbarsone toxicity: A review of the literature and report of 43 cases. *Ann Intern Med* 47:418-427, 1957.
16. Today's drugs: Drugs for dysentery. *Br Med J* 1:825-828, 1964.
17. Powell SJ: Drug therapy of amoebiasis. *Bull WHO* 40:953-956, 1969.
18. Khambatta RB: Metronidazole and the "symptomless cyst-passer." *Med Today* 3:72-74, 1969.
19. Chuttani PN, et al: The cyst passer. *Indian Practitioner* 21:714-718, 1968.
20. Chongsuphaisiddhi T, et al: Treatment of *Entamoeba histolytica* cyst passers with metronidazole. *Southeast Asian J Trop Med Public Health* 2:29-33, 1971.
21. Kanani SR, Knight R: Experiences with the use of metronidazole in the treatment of non-dysenteric intestinal amoebiasis. *Trans R Soc Trop Med Hyg* 66:244-249, 1972.
22. Powell SJ, Elsdon-Dew R: Chloroquine in amebic dysentery. *Trans R Soc Trop Med Hyg* 65:540, 1971.
23. Weber DM: Amebic abscess of liver following metronidazole therapy. *JAMA* 216:1339-1340, 1971.

## Treatment of non-invasive amoebiasis. A comparison between tinidazole alone and in combination with diloxanide furoate

PEHROLOV PEHRSON AND ELIAS BENGTTSSON

Dept. of Infectious Diseases, Karolinska Institute, Roslagstull Hospital, Box 5651, S-114 89 Stockholm, Sweden

### Summary

Tinidazole (40 mg/kg body-weight in one daily dose for five days) and tinidazole (same dose) plus diloxanide furoate (20 mg/kg body-weight divided into three daily doses for 10 days) were compared as treatments for amoebiasis. The parasitic cure rates were 44 and 91% respectively. We cannot, therefore, recommend tinidazole alone in this dosage as a treatment for non-invasive amoebiasis.

### Introduction

Tinidazole (Fasigyn) has recently been widely used as an alternative to metronidazole for the treatment of infections with *Entamoeba histolytica*. In a previous study (PEHRSON, 1982), tinidazole was given to a series of patients with chronic intestinal or asymptomatic amoebiasis. When checked by at least three stool specimens taken on different days, one month after treatment, we found a parasitic cure rate (p.c.r.) of 0% (0/14). This should be compared with the results obtained in other studies, showing a cure rate of 77 to 96% (MISRA & LAIQ, 1974; PRAKASH *et al.*, 1974; JOSHI & SHAH, 1975; BAKSHI *et al.*, 1978), using the same dosage schedule but mainly in cases of acute intestinal amoebiasis.

To investigate the reasons for the unsatisfactory response we obtained, which could be due to too low a dose or to a low efficiency of tinidazole in the gut lumen, we carried out a new trial with a higher daily dose of tinidazole and compared the effect of this higher dose with that following treatment with tinidazole and diloxanide furoate (Furamide) in combination. This latter was found to be an effective intraluminal amoebicide (WOODRUFF & BELL, 1960, 1967; WOLFE, 1973), whose mode of action upon the amoeba is unknown. We omitted Furamide as a single regimen, because it is considered to be ineffective against invasive amoebiasis and there is always a risk of developing an invasive form of the disease if zymodeme differentiation of strains of *Entamoeba histolytica* is not performed routinely (SARGEANT & WILLIAMS, 1978; SARGEANT *et al.*, 1982).

### Materials and Methods

During the period of the study, 41 patients were diagnosed as suffering from amoebiasis. All of them were supposed to have contracted their infections abroad, as amoebiasis is not considered to be endemic in Sweden. No cases of acute, dysenteric amoebiasis or diagnosed or suspected cases of liver abscess were included. The patients had not received any anti-amoebic drug during the previous year. Nine of the patients had a concomitant infection with *Giardia lamblia*, two with *Shigella flexneri*, two with *Campylobacter jejuni*, one with *Salmonella paratyphi A*, one with *Hymenolepis nana*, one with *Ascaris lumbricoides* and one with *Trichuris trichiura*.

In a predetermined, random order, the patients were allocated to two groups, 18 being treated with tinidazole alone and 23 with the combination. All were hospital in-patients and kept under supervision during treatment.

### Dosage schedules

- (1) tinidazole 40 mg/kg body-weight in one daily dose for five days;
- (2) tinidazole as above plus diloxanide furoate 20 mg/kg body-weight divided into three daily doses for 10 days.

Approximately one month after the treatment was completed, checks were made, including the examination of at least three stool specimens taken on different days. One of these was examined by direct microscopy of freshly passed, loose faeces induced by a 50% magnesium sulphate purgative and the other normally passed specimens were examined by the formol-ether-concentration technique described by RIDLEY & HAWGOOD (1956). Failure was defined as the persistence of amoebic trophozoites or cysts in any of these specimens.

Those in whom the treatment with tinidazole failed were later treated with the combination of tinidazole and diloxanide furoate and those in whom the combination failed were treated with metronidazole 40 mg/kg body-weight daily for 10 days.

### Results

Data on the participants and the results of the checks one month after treatment are shown in Table I. In no case were the side effects severe enough to cause cessation of treatment. Statistical analysis was made, using the chi-square test, and showed a significant difference between the two groups on the 1%-level (two-tailed test) and in favour of the combination. No differences could be found between the response of Swedes and that of the immigrants, or between those infected on different continents (Asia, Africa, South America). The presence of other parasites did not seem to affect the outcome of the treatment.

### Discussion

Our results with tinidazole alone (44% p.c.r.), in treating non-dysenteric amoebiasis, are unsatisfactory and differ very much from those obtained in previously published studies by different authors, using the same dosage schedules (77 to 96% p.c.r.) (ISLAM & HASAN, 1975; APTE & PACKARD, 1978) or lower (MISRA & LAIQ, 1974; PRAKASH *et al.*, 1974; JOSHI & SHAH, 1975; BAKSHI *et al.*, 1978). The patients in these studies were, however, mainly cases of acute amoebic dysentery, a factor which may have influenced the results.

A weak amoebicidal effect of the nitroimidazoles on the cyst stage of *E. histolytica* was observed by

Table I—Some characteristics and treatment results of 41 patients with non-invasive amoebiasis

| Treatment   | No. | Median age (age range) years | Patients with symptoms v. asymptomatics | Swedes v. other nationalities | Parasite-free at check | Parasite cure rate |
|---|-----|------------------------------|---|-------------------------------|------------------------|--------------------|
| Tinidazole 40 mg/kg × 1 + V                                     | 18  | 28 (9-68)                    | 11:7                                    | 8:10                          | 8                      | 44%                |
| Tinidazole 40 mg/kg × 1 × V + diloxanide furoate 500 mg × 3 × X | 23  | 26 (6-68)                    | 15:8                                    | 11:12                         | 21                     | 92%                |

SPILLMAN *et al.* (1976), but this report was contradicted by BAKSHI *et al.* (1978). Our drug trial was carried out in a country in which amoebiasis is not endemic, making reinfection during follow-up very unlikely, and confirming that the low p.c.r. was caused by "true" treatment failures.

We therefore believe that our poor results with tinidazole alone are due to its ineffectiveness in eradicating cysts in the lumen of the gut, either because of too effective absorption (MONRO, 1974) or inactivation by aerobic organisms as shown by RALPH & CLARKE (1978).

When tinidazole was combined with diloxanide furoate, we obtained a cure rate of 91%, which may be compared with studies by WOODRUFF & BELL (1967), in which they reported a cure rate of 95% in amoebic cyst-passers treated with diloxanide furoate alone for 10 days and WOLFE (1973), who found a cure rate of 83% using the same schedule. It is also noteworthy that all our failures with tinidazole alone have proved to be freed from their infection after treatment with the combination.

#### Acknowledgements

We wish to thank Mrs. Inger Pontén, the head nurse in the tropical ward and Birgit Lindberg, the chief technician at the laboratory of tropical diseases, for their devoted work with the patients.

#### References

- Apte, V. V. & Packard, R. S. (1978). Tinidazole in the treatment of trichomoniasis, giardiasis and amoebiasis. Report of a multicentre study. *Drugs*, 15 (Suppl. 1), 43-48.
- Bakshi, J. S., Ghiara, J. M. & Nanivadekar, A. S. (1978). How does Tinidazole compare with Metronidazole? A summary report of Indian trials in amoebiasis and giardiasis. *Drugs*, 15 (Suppl. 1), 33-42.
- Islam, N. & Hasan, M. (1975). Tinidazole in the treatment of intestinal amoebiasis. *Current Therapeutic Research*, 17, 161-165.
- Joshi, H. D. & Shah, B. M. (1975). A comparative study of tinidazole and metronidazole in treatment of amoebiasis. *Indian Practitioner*, 28, 295-302.
- Misra, N. P. & Laiq, S. M. (1974). Comparative trial of tinidazole and metronidazole in intestinal amoebiasis. *Current Therapeutic Research*, 16, 1255-1263.
- Monro, A. H. (1974). Blood levels of chemotherapeutic drugs and the pharmacokinetics of tinidazole and metronidazole. *Current Medical Research and Opinion*, 2, 130-136.
- Pehrson, P. O. (1982). The treatment of non-invasive amoebiasis—a comparison between metronidazole and tinidazole. *Annals of Tropical Medicine and Parasitology*.
- Prakash, C., Bansal, B. C. & Bansal, M. R. (1974). Tinidazole in symptomatic intestinal amoebiasis. *Journal of Tropical Medicine and Hygiene*, 77, 165-167.
- Ralph, E. D. & Clark, D. A. (1978). Inactivation of metronidazole by anaerobic and aerobic bacteria. *Antimicrobial Agents and Chemotherapy*, 14, 377-383.
- Ridley, D. S. & Hawgood, B. C. (1956). The value of formol-ether concentration of faecal cysts and ova. *Journal of Clinical Pathology*, 9, 74-76.
- Sargeant, P. G. & Williams, J. E. (1978). The differentiation of invasive and non-invasive *Entamoeba histolytica* by isoenzyme electrophoresis. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 72, 519-521.
- Sargeant, P. G., Jackson, T. F. H. G. & Srimjee, A. (1982). Biochemical homogeneity of *Entamoeba histolytica* isolates, especially those from liver abscess. *Lancet*, i, 1386-1388.
- Spillman, R., Ayala, S. C. & de Sanchez, C. E. (1976). Double blind test of metronidazole and tinidazole in the treatment of asymptomatic *Entamoeba histolytica* and *Entamoeba hartmanni* carriers. *American Journal of Tropical Medicine and Hygiene*, 25, 549-551.
- Wolfe, M. S. (1973). Nondysenteric intestinal amoebiasis. Treatment with diloxanide furoate. *Journal of the American Medical Association*, 244, 1601-1604.
- Woodruff, A. W. & Bell, S. (1960). Clinical trials with entamide furoate and related compounds: I In a non-tropical environment. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 54, 389-395.
- Woodruff, A. W. & Bell, S. (1967). The evaluation of amoebicides. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 61, 435-439.

Accepted for publication 30th March, 1983.

**A. INGREDIENT NAME:**

**CHOLINE BITARTRATE NF XI**

**B. Chemical Name:**

Choline Acid Tartrate, Bitartarato de Colina, 2-Hydroxyethyltrimethylammonium hydrogen tartrate, (2-Hydroxyethyl)trimethylammonium Bitartrate

**C. Common Name:**

Colyne

**D. Chemical grade or description of the strength, quality, and purity of the ingredient:**

|       | <i>(Minimum)</i> | <i>(Result)</i> |
|-------|------------------|-----------------|
| Assay | 98.0%            | 99.7%           |

**E. Information about how the ingredient is supplied:**

White Crystalline Powder, odorless of faint trimethylamine-like odor, acid taste, hygroscopic

**F. Information about recognition of the substance in foreign pharmacopeias:**

Braz., Ger., Nord., and Port.

**G. Bibliography of available safety and efficacy data including peer reviewed medical literature:**

Fovall, P., Dysken, M. W., and Lazarus, L. W. Choline bitartrate treatment of Alzheimer-type dementia. *Communications in Psychopharmacology*, 1980; 4(2): 141-145.

Beauregard, W. G. Dexpanthenol with choline bitartrate in the treatment of infantile colic. *Journal of the Louisiana State Medical Society*, 1968; 120(3): 142-145.

**H. Information about dosage forms used:**

Capsules

Tablets

**I. Information about strength:**

Capsules (500mg-2gm)

Tablets (500gm-600gm)

**J. Information about route of administration:**

Orally

**K. Stability data:**

Melts at about 150-151°

**L. Formulations:**

**M. Miscellaneous Information:**

CERTIFICATE OF ANALYSIS

301343

# 50730

PRODUCT: CHOLINE BITARTRATE  
RELEASE #: 103145

(UNCOATED)  
LOT # :B60688F13

GRADE: N.F. XI  
CODE:V9612160170

SPECIFICATIONS

RESULT

| DESCRIPTION                | WHITE CRYSTALLINE POWDER | CONFORMS    |
|----------------------------|--------------------------|-------------|
| Identification             | To pass test             | Passes test |
| Water                      | 0.5% max.                | 0.02%       |
| Residue on ignition        | 0.1% max.                | < 0.1%      |
| Heavy metals               | 20 ppm max.              | < 20 ppm    |
| Assay<br>(anhydrous basis) | 98.0% min.               | 99.7%       |

0

ATTENTION: TONY HATCHETT

Date :06/05/97

Prepared by : A. Whitney

10650

Approved by : 

6/97

Our Order # 233927-1 Your PO # 52325

QUALITY CONTROL REPORT

CHEMICAL NAME.: CHOLINE BITARTRATE N.F. \_\_\_\_\_

MANUFACTURE LOT NO.: B62966M18

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP \_\_\_/BP \_\_\_/NF \_\_\_/MERCCK \_\_\_/MART. \_\_\_/CO. SPECS. \_\_\_.

1) DESCRIPTION.:

E WHITE CRYSTALLINE POWDER; ODORLESS OR FAINT TRIMETHYLAMINE-LIKE ODOR; ACID TASTE; HYGROSCOPIC.

2) SOLUBILITY.:

SOLUBLE IN WATER AND IN ALCOHOL; INSOLUBLE IN ETHER, CHLOROFORM AND BENZENE.

3) MELTING POINT.:

- K MELTS AT ABOUT 150-151 DEGREES.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

- A) COMPLIES (A) AS PER NF 10th PAGE 154.
- B) COMPLIES (B) AS PER NF 10th PAGE 154.
- C) COMPLIES (C,D) AS PER NF 10th PAGE 154.

PASSES.: \_\_\_\_\_

FAILS.: \_\_\_\_\_

COMMENTS.:

ANALYST SIGNATURE.: \_\_\_\_\_

DATE.: \_\_\_\_\_

PREPACK TEST.: \_\_\_\_\_

DATE.: \_\_\_\_\_

INITIAL.: \_\_\_\_\_

RETEST.: \_\_\_\_\_

DATE.: \_\_\_\_\_

INITIAL.: \_\_\_\_\_

----- IDENTIFICATION -----

PRODUCT #: 34449-4      NAME: CHOLINE BITARTRATE, 99%  
CAS #: 87-67-2  
MF: C9H19NO7

----- TOXICITY HAZARDS -----

DATA NOT AVAILABLE

----- HEALTH HAZARD DATA -----

ACUTE EFFECTS

MAY BE HARMFUL BY INHALATION, INGESTION, OR SKIN ABSORPTION.  
CAUSES EYE AND SKIN IRRITATION.  
MATERIAL IS IRRITATING TO MUCOUS MEMBRANES AND UPPER  
RESPIRATORY TRACT.  
TO THE BEST OF OUR KNOWLEDGE, THE CHEMICAL, PHYSICAL, AND  
TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY INVESTIGATED.

FIRST AID

IN CASE OF CONTACT, IMMEDIATELY FLUSH EYES WITH COPIOUS AMOUNTS  
OF

WATER FOR AT LEAST 15 MINUTES.

IN CASE OF CONTACT, IMMEDIATELY WASH SKIN WITH SOAP AND COPIOUS

AMOUNTS OF WATER.

IF INHALED, REMOVE TO FRESH AIR. IF NOT BREATHING GIVE ARTIFICIAL  
RESPIRATION. IF BREATHING IS DIFFICULT, GIVE OXYGEN.

IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS  
CONSCIOUS.

CALL A PHYSICIAN.

WASH CONTAMINATED CLOTHING BEFORE REUSE.

----- PHYSICAL DATA -----

MELTING PT: 151 C TO 153 C

APPEARANCE AND ODOR

WHITE POWDER

----- FIRE AND EXPLOSION HAZARD DATA -----

EXTINGUISHING MEDIA

WATER SPRAY.

CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.

SPECIAL FIREFIGHTING PROCEDURES

WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING  
TO

PREVENT CONTACT WITH SKIN AND EYES.

UNUSUAL FIRE AND EXPLOSIONS HAZARDS

EMITS TOXIC FUMES UNDER FIRE CONDITIONS.

----- REACTIVITY DATA -----

INCOMPATIBILITIES

STRONG OXIDIZING AGENTS

PROTECT FROM MOISTURE.  
HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS  
TOXIC FUMES OF:  
CARBON MONOXIDE, CARBON DIOXIDE  
NITROGEN OXIDES

----- SPILL OR LEAK PROCEDURES -----

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED  
WEAR RESPIRATOR, CHEMICAL SAFETY GOGGLES, RUBBER BOOTS AND  
HEAVY  
RUBBER GLOVES.  
SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.  
AVOID RAISING DUST.  
VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS  
COMPLETE.

WASTE DISPOSAL METHOD

DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN  
IN A  
CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.

--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---

CHEMICAL SAFETY GOGGLES.  
COMPATIBLE CHEMICAL-RESISTANT GLOVES.  
NIOSH/MSHA-APPROVED RESPIRATOR.  
SAFETY SHOWER AND EYE BATH.  
MECHANICAL EXHAUST REQUIRED.  
DO NOT BREATHE DUST.  
AVOID CONTACT WITH EYES, SKIN AND CLOTHING.  
WASH THOROUGHLY AFTER HANDLING.  
IRRITANT.  
KEEP TIGHTLY CLOSED.  
HYGROSCOPIC  
STORE IN A COOL DRY PLACE.  
IRRITATING TO EYES, RESPIRATORY SYSTEM AND SKIN.  
IN CASE OF CONTACT WITH EYES, RINSE IMMEDIATELY WITH PLENTY OF

WATER AND SEEK MEDICAL ADVICE.

WEAR SUITABLE PROTECTIVE CLOTHING.

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT  
PURPORT TO BE  
ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA ALDRICH SHALL  
NOT BE  
HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM  
CONTACT WITH THE  
ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR

—  
ADDITIONAL  
TERMS AND CONDITIONS OF SALE

behaviour appeared to improve in 2 patients in the first 24 hours of the study. A dose of 10 g daily produced nausea, diarrhoea, and a small reduction in blood pressure.— W. D. Boyd *et al.* (letter), *Lancet*, 1977, 2, 711.

Choline bitartrate had no beneficial effect in 3 elderly patients with Alzheimer's disease. One patient became incontinent with foul odour.— P. Etienne *et al.* (letter), *Lancet*, 1978, 1, 508.

In a double-blind placebo-controlled crossover study, 3 of 10 patients with Alzheimer's disease seemed less confused following administration of choline 9 g daily (as the bitartrate) for 2 weeks. Exacerbation of pre-existing urinary incontinence occurred in 3 patients, and some patients suffered gastro-intestinal discomfort; an additional patient, whose diagnosis was changed to depression, felt more depressed. Although the results were not encouraging, possible benefit from choline therapy could not be ruled out; it was considered that the dose used was too high.— C. M. Smith *et al.* (letter), *Lancet*, 1978, 2, 318. Initial encouraging results had been obtained following administration of choline dihydrogen citrate 9 g daily for 21 days to younger patients (under 65 years) with early Alzheimer's disease.— J. L. Signoret *et al.* (letter), *ibid.*, 1978, 2, 837.

The pathogenesis of Alzheimer's disease.— D. M. Bowen *et al.*, *Lancet*, 1979, 1, 11; I. Grundke-Iqbal *et al.*, *Lancet*, 1979, 1, 578.

In a double-blind study of 18 women with Alzheimer's disease there was no beneficial effect when choline chloride 15 g daily was taken for 2 months.— E. B. Renvoize and T. Jerram (letter), *New Engl. J. Med.*, 1979, 301, 330.

Concomitant use of piracetam and choline in patients with senile dementia of the Alzheimer's type.— E. Friedman *et al.* (letter), *New Engl. J. Med.*, 1981, 304, 1490.

See also under Lecithins, p.55.

**Ataxia.** A 56-year-old man with cerebellar ataxia improved dramatically while taking choline 4 or 5 g daily.— N. J. Legg, *Br. med. J.*, 1978, 2, 1403. An earlier report of improvement in cerebellar ataxia in a patient treated with choline chloride had not been confirmed in a further 13 patients; they had not benefited.— N. Legg (letter), *Br. med. J.*, 1979, 2, 133.

None of 6 patients with hereditary ataxia benefited from treatment with choline chloride 1 g four times daily for a week followed, after a 2-week rest, by treatment for a month.— D. V. Philcox and B. Kies (letter), *Br. med. J.*, 1979, 2, 613.

Preliminary results of a double-blind crossover study in 8 patients with Friedreich's ataxia, 6 with sporadic cerebellar degeneration, and 6 with atypical spinocerebellar degeneration with cerebellar ataxia and spasticity of the lower limbs showed some improvement in upper limb coordination after treatment with choline 6 or 12 g daily but only 2 patients had improvement in gait.— I. R. Livingstone and F. L. Mastaglia (letter), *Br. med. J.*, 1979, 2, 939.

**Blepharospasm.** Possible benefit of choline in blepharospasm.— B. Skarf and J. A. Sharpe (letter), *New Engl. J. Med.*, 1981, 305, 957.

**Deficiency states.** Evidence of choline deficiency in 15 patients receiving total parenteral nutrition.— M. E. Burt *et al.* (letter), *Lancet*, 1980, 2, 638.

**Gilles de la Tourette's syndrome.** For choline therapy in Gilles de la Tourette's syndrome see under Lecithins, p.55.

**Huntington's chorea.** In 5 patients with Huntington's chorea choline chloride 3 to 15 g daily produced dose-dependent elevation of free choline in plasma but had little or no effect on symptoms.— S. -M. Aquilonius and S. -A. Eckernas, *Neurology, Minneap.*, 1977, 27, 887.

**Tardive dyskinesia.** In a double-blind placebo-controlled study of 20 patients with tardive dyskinesia choline chloride 150 mg per kg body-weight daily (in 3 divided doses) for 1 week increased to 200 mg per kg daily for a second week, decreased choreic movements in 9, increased them in 1, and had no effect in 10. Plasma concentrations of choline increased from a range of 8.6 to 20.5 nmol per ml before treatment to 18.2 to 60.1 nmol per ml 1 hour after a dose in the second week.— J. H. Grawdon *et al.*, *New Engl. J. Med.*, 1977, 297, 524.

In 5 patients with tardive dyskinesia choline chloride 150 to 200 mg per kg body-weight daily in divided doses, or lecithin 21 to 105 g daily, reduced abnormal movements. The bitter taste of choline, the development of a fishy odour, and gastro-intestinal effects made lecithin preferable.— A. J. Gelenberg *et al.*, *Am. J. Psychiat.*, 1979, 136, 772.

Further references: *Med. Lett.*, 1979, 21, 34.

**Trimethylaminuria.** Adjustment of the diet to lower the intake of choline to a minimal safety concentration was effective within 3 weeks in controlling the production of trimethylamine in a 13-year-old boy who had been suffering from a fishy odour for about 7 years. While trimethylamine was still excreted in the urine it was barely detectable in the sweat and breath.— R. Marks *et al.*, *Br. J. Derm.*, 1976, 95, Suppl. 14, 11.

Choline bitartrate 5 g given in 3 doses at 8-hourly intervals had been found useful as a diagnostic aid for patients with trimethylaminuria.— R. Marks *et al.*, *Br. J. Derm.*, 1977, 96, 399.

**Proprietary Names**  
Neurotropan (Itting, Ger.).

7874-v

**Choline Bitartrate. Choline Acid Tartrate. Bitartrato de Colina. 2-Hydroxyethyltrimethylammonium hydrogen tartrate.**  
 $C_9H_{19}NO_7=253.3$

CAS — 87-67-2.

**Pharmacopoeias.** In *Braz., Ger., Nord., and Port.*

A white, hygroscopic, crystalline powder with an acid taste and a faint amine-like odour. Very soluble in water; slightly soluble in alcohol; very slightly soluble in acetone and light petroleum; practically insoluble in chloroform and ether. Solutions are sterilised by autoclaving or by filtration. Store in airtight containers.

Uses. Choline bitartrate has the same actions as choline, p.1651.

**Proprietary Names**  
Colyne (see also under Choline Chloride) (Saita, Ital.).

7875-g

**Choline Chloride. Cholinii Chloridum. 2-Hydroxyethyltrimethylammonium chloride.**  
 $C_9H_{14}ClNO=139.6$

CAS — 67-48-1.

**Pharmacopoeias.** In *Aust., Belg., Cz., Ger., Hung., and It.*

White, odourless, tasteless, very hygroscopic crystals. Very soluble in water and alcohol; very slightly soluble in acetone and light petroleum; practically insoluble in chloroform and ether. A 10% solution in water has a pH of 5 to 6. Solutions may be sterilised by filtration. Store in airtight containers.

Uses. Choline chloride has the same actions as choline, p.1651.

**Proprietary Names**  
Becholine (Medical Research, Austral.); Becholine D (Medical Research, Austral.); Colyne (see also under Choline Bitartrate) (Saita, Ital.).

7876-q

**Choline Dihydrogen Citrate. Choline Citrate. Cholinum Citricum. Citrato de Colina. 2-Hydroxyethyltrimethylammonium dihydrogen citrate.**  
 $C_{11}H_{21}NO_8=295.3$

CAS — 77-91-8.

**Pharmacopoeias.** In *Belg. and Pol.*

Colourless translucent hygroscopic crystals or white crystalline powder with an acid taste; it is odourless or has a faint amine-like odour. Soluble 1 in 1 of water and 1 in 45 of alcohol; very slightly soluble in chloroform and ether. A 25% solution in water has a pH of 3.5 to 4.5. Store in airtight containers.

Uses. Choline dihydrogen citrate has the same actions and uses as choline, p.1651.

**Cystinuria.** For a report of choline dihydrogen citrate being given to facilitate enzymic remethylation of homocystine to methionine in the treatment of homocystinuria, see Cystine, p.50.

**Proprietary Preparations**  
Wallachol (Wallace Mfg Chem., UK; Farillon, UK). Syrup containing in each 100 ml choline dihydrogen

citrate 4.5 g, the antitoxic principle from 7.5 liver, proteolysed liver equivalent to fresh racemethionine 375 mg, inositol 500 mg, hydrochloride 20 mg, riboflavine 5 mg, hydrochloride 5 mg, cyanocobalamin 50 µg, a amide 100 mg. Tablets each containing choline citrate 224 mg, the antitoxic principle 250 mg of fresh liver, dried liver 50 mg, race 112 mg, inositol 56 mg, thiamine hydrochloride 1 mg, pyridoxine hydrochloride 250 µg, cobalamin 1 µg, and nicotinamide 5 mg. For function and impaired fat metabolism. Do 15 ml of syrup, or 2 or 3 tablets, thrice daily.

7877-p

**Inositol. i-Inositol; meso-Inositol. myo-Inositol.**  
 $C_6H_{12}O_6=180.2$

CAS — 87-89-8.

**Pharmacopoeias.** In *Aust., Belg., and Chin.* Odourless fine white crystals or white crystalline powder with a sweet taste. M.p. about 224°. It is optically inactive. Soluble 1 in 6 of water; slightly soluble in alcohol; practically insoluble in chloroform and ether. In water are neutral to litmus.

Inositol is present in animal tissues and in plants, especially in seeds and cereal brans.

Apart from its presence in organic matter in various forms, little is known about the specific functions of inositol, though it is stated to be curative of moxycitric acid and to be capable of preventing fatty liver. It is an essential nutrient for some micro-organisms. Deficiency symptoms in mice have been cured by 10 mg of inositol in 100 g of food. Most purified inositol used for experimental purposes contain this level. Its role in human nutrition is unknown. The consumption of inositol by man is about 1 g daily. Preliminary findings following administration of 500 mg twice daily to 7 diabetic subjects for 2 weeks suggested that it might be beneficial in the treatment of diabetic neuropathy.— J. G. Salway *et al.*, *Diabetologia*, 1978, 2, 1282.

**Tablet excipient.** Inositol was considered suitable as an excipient for chewable tablets because it was tasteless, inert, non-toxic, and physically stable. — Nasir and L. O. Wilken, *J. pharm. Sci.*, 1966, 55, 1066.

**Proprietary Preparations**  
Inositol Capsules (Bioglan, UK). Each contains 100 mg.

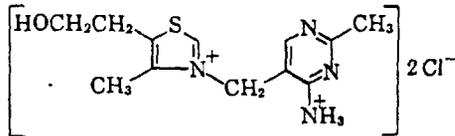
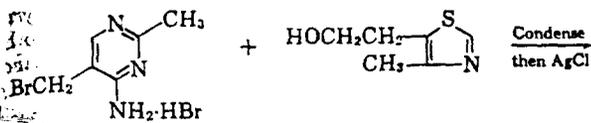
**Other Proprietary Names**  
Inosital, Inositina (both Ital.); Inosit-Zyma (Ger.).

7878-s

**Compound Preparations of Vitamin B Group**

**Compound Vitamin B Tablets (B.P.C. 1973).** Each contains Thiamine Tablets; Compound Aneurine Tablets; Vitamin B Compound Tablets. Each contains thiamine hydrochloride 15 mg, riboflavine 1 mg, and thiamine hydrochloride 1 mg. Store in airtight containers and avoid contact with metal. Protect from light. Dose. Prophylactic: 2 tablets daily.

**Strong Compound Vitamin B Tablets (B.P.C. 1973).** Each contains Thiamine Tablets; Strong Compound Aneurine Tablets; Strong Vitamin B Compound Tablets. Each contains nicotinamide 20 mg, pyridoxine hydrochloride 2 mg, riboflavine 2 mg, and thiamine hydrochloride 5 mg. They may be coated. Store in airtight containers and avoid contact with metal. Protect from light. Dose. Therapeutic, 1 or 2 tablets thrice daily. **Vitamins B and C Injection (B.P.C. 1973).** A solution of vitamins B and C in Water for Injection, immediately before use, by mixing the contents of a pair of ampoules. Sterilised by autoclaving, maintaining at 98° to 100° for 30 minutes. Each ampoule contains 50 mg of ascorbic acid, 50 mg of riboflavine sodium phosphate 4 mg, and thiamine hydrochloride 250 mg in 5 ml, and the other containing a solution of ascorbic acid (as so



Thiamine Chloride Hydrochloride (the official vitamin)

**Description**—Small white crystals or a crystalline powder usually having a slight, characteristic odor. When exposed to air, the anhydrous product rapidly absorbs about 4% of water. Its solutions are acid to litmus paper. The pH of a solution (1 in 100) is between 2.7 and 3.4. It is stable, with some decomposition, at about 248°.

**Solubility**—1 Gm dissolves in about 1 ml of water and about 100 ml of alcohol; soluble in glycerin; insoluble in ether or benzene.

**Incompatibilities**—Thiamine Hydrochloride in the dry state is stable. Acidic solutions having a pH below 5.5, preferably from 5.0 to 3.5, are also relatively stable. Alkalies destroy it. It is precipitated from solution by several of the alkaloidal reagents such as mercuric chloride, iodine, ferric acid, tannin, and Mayer's reagent. It is sensitive to oxidizing and reducing agents.

Solutions of thiamine hydrochloride are necessarily acid in reaction and are, therefore, incompatible with any acidifying substance. Phenobarbital sodium has been an occasional offender in this respect, the result frequently being that as to cause precipitation of the phenobarbital as well as a partial lowering of the acidity of the mixture with consequent deterioration of the vitamin. Phenobarbital, not the sodium derivative, may be dispensed in such an instance provided that sufficient alcohol is present to keep it in solution. If a part of the elixir is replaced with alcohol for any purpose, an amount of thiamine hydrochloride equivalent to that contained in the volume so replaced must be added to the product.

**Uses**—For a description of the metabolic functions and of a deficiency, see *Thiamine* (page 1033). Thiamine is used to treat beriberi and also general B vitamin deficiency. The fact that thiamine cures the neuro-pathologies of beriberi has given rise to a widespread use of thiamine in nearly any type of neuropathology. Although such indiscriminatory use can do no organic harm to the patient, it constitutes an unnecessary expense; the promotion of the vitamin for such promiscuous use constitutes an abuse.

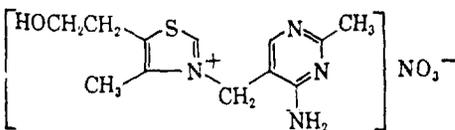
**Dose**—Oral or parenteral, daily, 2 to 100 mg; usual, prophylactic, 2 mg once a day; therapeutic, 10 to 15 mg, 2 or 3 times a day.

**Dosage Forms**—Injection USP: 100 mg/ml, 200 mg/2 ml, 500 mg and 1 Gm/10 ml, 2 Gm/20 ml, 2.5 Gm/5, 10, and 25 ml, 3 and 6 Gm/30 ml; Tablets USP: 5, 10, 25, 50, 100, and 250 mg.

**Veterinary Dose** (not well established)—Prophylactic, Horses, 2.5 mg per 100 pounds of body weight; Dogs, 0.3 to 0.6 mcg per pound of body weight; therapeutic, Dogs, 0.6 to 2 mg daily.

### Thiamine Mononitrate USP

[Thiamine Nitrate; Vitamin B<sub>1</sub> Mononitrate]



Thiamine Mononitrate contains 98.0–102.0% of C<sub>12</sub>H<sub>17</sub>N<sub>5</sub>O<sub>4</sub>S (327.36), calculated on the dried basis.

**Description**—White crystals or crystalline powder, usually having a slight, characteristic odor.

**Solubility**—1 Gm dissolves in about 35 ml of water; slightly soluble in alcohol and chloroform.

**Uses**—Thiamine Mononitrate is more stable than thiamine hydrochloride. Its vitaminergic actions and uses are identical to those of the hydrochloride. See *Thiamine Hydrochloride* (this page) and the general statement on *Thiamine* (page 1033).

### Other Water-Soluble Vitamins

**Aminobenzoic Acid NF XII** [*p*-Aminobenzoic Acid; PABA], dried at 105° for 2 hours, contains not less than 98.5% of C<sub>7</sub>H<sub>7</sub>NO<sub>2</sub> (137.14). The aminobenzoic acid of biological significance is para-aminobenzoic acid (PABA).

**Preparation**: From *p*-nitrobenzoic acid by reduction with iron and hydrochloric acid. The required *p*-nitrobenzoic acid is obtained by oxidation of the readily available *p*-nitrotoluene with potassium permanganate or potassium dichromate in the presence of sulfuric acid. **Description and Solubility**: White or slightly yellow, odorless crystals or a crystalline powder. It discolors on exposure to air or light. It melts between 186° and 189°.

**Uses**: PABA is an essential nutrient for a number of microorganisms, especially those that synthesize folic acid. The failure of growth of rats, chicks and mice, and achromotrichia in black rats has been observed in the absence of PABA. Consequently, PABA has long been included among the vitamins. However, it now appears that the nutrient action is indirect, mediated through folic acid and other vitamins synthesized by enteric bacteria. Since mammals utilize preformed folic acid, PABA is not required in the diet to support the biosynthesis of folic acid, and no other biological loci for the compound have been shown. Consequently, there is no need for PABA in human nutrition, and continued promotion of the compound represents an abuse. For this reason Aminobenzoic Acid has been dropped from the NF. Aminobenzoic Acid acts as a sun screen and is incorporated into some sunscreen ointments.

**Calcium Leucovorin USP XVI** [(Lederle); Calcium Folate-SF; Calcium 5-Formyl-5,6,7,8-tetrahydrofolate; Calcium *N*-[*p*-[[2-Amino-5-formyl-5,6,7,8-tetrahydro-4-hydroxy-6-pteridyl)methyl]amino]benzoyl]glutamate; Citrovorum Factor]—Purity: 90–110% of C<sub>22</sub>H<sub>27</sub>CaN<sub>7</sub>O<sub>7</sub>·5H<sub>2</sub>O. A yellowish white or yellow, odorless, microcrystalline powder. Very soluble in water; practically insoluble in alcohol. **Uses**: Leucovorin (folic acid) is the biological formyl derivative and the active form of folic acid (see *Folic Acid*), and the calcium salt is simply a convenient pharmaceutical form that is preferred for intramuscular injection. Consequently its uses and limitations in the treatment of the megaloblastic anemias are the same as for folic acid. However, it is superior to folic acid in counteracting the excessive effects of the folic acid antagonists (methotrexate, etc; see page 1169), since the antagonists competitively antagonize the conversion of folic acid to leucovorin and not the leucovorin itself. **Dose**: Intramuscularly, for the counteraction of folic acid antagonists, 3 to 6 mg daily; for the treatment of megaloblastic anemias, 10 mg daily for 10 to 15 days; as an adjunct to cyanocobalamin therapy, 0.2 to 15 mg daily.

**Choline Bitartrate NF XI** [(2-Hydroxyethyl)trimethylammonium Bitartrate]\*—A white, crystalline powder. It is hygroscopic when exposed to air. It is freely soluble in water and slightly soluble in alcohol; insoluble in ether, chloroform, and benzene. **Uses**: See *Choline Chloride* (this page). The bitartrate anion does not affect the physiological actions of choline. **Dose**: 2 Gm. [\*C<sub>5</sub>H<sub>15</sub>NO<sub>3</sub>.]

**Choline Chloride** is (2-hydroxyethyl)trimethylammonium chloride.† **Preparation**: For the preparation of choline, see *Choline Dihydrogen Citrate* (below). **Description and Solubility**: White, deliquescent crystals. A 10% aqueous solution has a pH of about 4.7. Very soluble in water or alcohol. **Uses**: For the metabolic effects of *Choline*, see the general statement (page 1026). Choline Chloride is used to reduce fatty infiltration of the liver and thus supposedly to

of water, and acidify with nitric acid; filter, and add to the filtrate, silver nitrate T.S.: a copious, white precipitate is produced, which is soluble in ammonia T.S.

**Melting range**—Chlorothymol melts between 59° and 61°, page 691.

**Reaction**—Agitate 500 mg. of Chlorothymol with 10 ml. of hot water: the liquid is neutral to litmus.

**Residue on ignition**—Chlorothymol yields not more than 0.05 per cent of residue on ignition, page 711.

**Packaging and storage**—Preserve Chlorothymol in well-closed, light-resistant containers, and avoid continuous excessive heat.

**CATEGORY**—Antibacterial.

### Choline Bitartrate

## CHOLINE BITARTRATE

2-Hydroxyethyl-trimethylammonium Bitartrate

$C_9H_{19}NO_7$                        $[\text{HOCH}_2\text{CH}_2\text{N}^+(\text{CH}_3)_3]\text{HC}_4\text{H}_4\text{O}_6^-$                       Mol. wt. 253.26

Choline Bitartrate, dried in a vacuum desiccator over phosphorus pentoxide for 4 hours, yields not less than 98 per cent of  $C_9H_{19}NO_7$ .

**Description**—Choline Bitartrate occurs as a white, crystalline powder. It is odorless or it may have a faint trimethylamine-like odor. It has an acidic taste. It is hygroscopic.

**Solubility**—Choline Bitartrate is freely soluble in water and slightly soluble in alcohol. It is insoluble in ether, in chloroform, and in benzene.

**Identification**—

**A:** Dissolve 500 mg. of Choline Bitartrate in 2 ml. of water, add 3 ml. of sodium hydroxide T.S., and heat to boiling: the odor of trimethylamine is detectable.

**B:** Dissolve 500 mg. of Choline Bitartrate in 2 ml. of iodine T.S.: a reddish brown precipitate is immediately formed. Add 5 ml. of sodium hydroxide T.S.: the precipitate dissolves and the solution becomes a clear yellow. Heat the solution to boiling: a pale yellow precipitate forms and the odor of iodoform may be detected.

**C:** To 2 ml. of cobaltous chloride T.S. add 1 ml. of a solution of Choline Bitartrate (1 in 100) and 2 ml. of potassium ferrocyanide solution (1 in 50): an emerald green color develops immediately.

**D:** Choline Bitartrate solution responds to the tests for *Tartrate*, page 685.

**Water**—Determine the water content by drying about 500 mg. of Choline Bitartrate, accurately weighed, in a vacuum desiccator over phosphorus pentoxide for 4 hours or by the Karl Fischer method, page 737, using a 2-Gm. sample dissolved in 50 ml. of anhydrous methanol: it contains not more than 0.5 per cent of water.

**Residue on ignition**—Choline Bitartrate contains not more than 0.1 per cent of residue on ignition, page 711.

**Heavy metals**—Dissolve 2 Gm. of Choline Bitartrate in 20 ml. of water, add 2 ml. of diluted hydrochloric acid, and dilute to 25 ml. with water: the heavy metals limit, page 673, for Choline Bitartrate is 20 parts per million.

**Assay**—Weigh accurately about 100 mg. of Choline Bitartrate, previously dried in a vacuum desiccator over phosphorus pentoxide for 4 hours. Dissolve it in 40 ml. of water in a 150-ml. beaker, and carefully add 10 ml. of freshly prepared saturated ammonium reineckate solution from a pipette, allowing it to run down the side of the beaker so that it forms a layer under the choline solution without producing turbulence. Mix by rotating the beaker gently and allow to stand in a refrigerator for one hour, rotating the beaker from time to time. Filter, collect the precipitate

**Choline Bitartrate Capsules** H J

Choline Bitartrate Capsules contain not less than 93 per cent and not more than 107 per cent of the labeled amount of  $C_9H_{19}NO_7$ .

**Identification—**

**A:** Dissolve the contents of a sufficient number of Choline Bitartrate Capsules, equivalent to about 2 Gm. of choline bitartrate, in 20 ml. of water, and filter the solution: a 5-ml. portion of the filtrate responds to *Identification test B* under *Choline Bitartrate*, page 87.

**B:** Dilute 1 ml. of the filtrate obtained in *Identification test A* to 10 ml. with water: the resulting solution responds to *Identification test C* under *Choline Bitartrate*, page 87.

**C:** The remainder of the filtrate obtained under *Identification test A* responds to the tests for *Tartrate*, page 434.

**Weight variation**, page 467—Choline Bitartrate Capsules meet the requirements of the weight variation test for capsules.

**Assay**—Transfer, as completely as possible, the contents of not less than 20 Choline Bitartrate Capsules to a 250-ml. beaker. Add 100 ml. of water and stir to dissolve the choline bitartrate. Filter the solution through paper into a 1000-ml. volumetric flask. Place the emptied capsules in the same beaker, add sufficient water to cover them, agitate for 5 minutes, and transfer the contents of the beaker to the filter. Wash the beaker and filter with several portions of water, adding the washings to the flask. Finally, add water to make exactly 1000 ml., and mix well. Transfer an accurately measured aliquot of the solution, equivalent to about 100 mg. of choline bitartrate, to a 150-ml. beaker, add sufficient water to make 40 ml., and proceed as directed in the *Assay* under *Choline Bitartrate*, page 87, beginning with "...carefully add 10 ml. of freshly prepared saturated ammonium reineckate solution..." The weight of choline reineckate multiplied by 0.5993 gives the equivalent weight of  $C_9H_{19}NO_7$ .

**Packaging and storage**—Preserve Choline Bitartrate Capsules in tight containers.

**Capsules available**—Choline Bitartrate Capsules usually available contain the following amount of choline bitartrate: 500 mg. I

**CATEGORY and DOSE**—See Choline Bitartrate.

**Choline Bitartrate Tablets** H J

Choline Bitartrate Tablets contain not less than 95 per cent and not more than 105 per cent of the labeled amount of  $C_9H_{19}NO_7$ .

**Identification—**

**A:** A filtered solution of Choline Bitartrate Tablets, representing a concentration of choline bitartrate (1 in 10), responds to *Identification test B* under *Choline Bitartrate*, page 87.

**B:** Dilute 1 ml. of the above solution to 10 ml. with water: the resulting solution responds to *Identification test C* under *Choline Bitartrate*, page 87.

**C:** The solution obtained under *Identification test A* responds to the tests for *Tartrate*, page 434.

**Disintegration**, page 455—The disintegration time limit for Choline Bitartrate Tablets is 1 hour.

**Weight variation**, page 468—Choline Bitartrate Tablets meet the requirements of the weight variation test for tablets.

**Assay**—Weigh and finely powder not less than 20 Choline Bitartrate Tablets. Weigh accurately a portion of the powder, equivalent to about 1 Gm. of choline bitartrate, and dissolve it in about 25 ml. of water. Filter the solution through paper into a 100-ml. volumetric flask. Add sufficient water through the filter to make exactly 100 ml. Transfer a 10-ml. aliquot of this solution, equivalent to approximately 100 mg. of choline bitartrate, to a 100-ml. beaker, add water to make 40 ml., and proceed as directed in the *Assay* under *Choline Bitartrate*, page 87, beginning with "...carefully add 10 ml. of freshly prepared, saturated ammonium reineckate solution..." The weight of choline reineckate multiplied by 0.5993 represents the equivalent weight of  $C_9H_{19}NO_7$ .

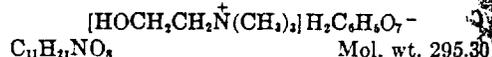
**Packaging and storage**—Preserve Choline Bitartrate Tablets in tight containers.

**Tablets available**—Choline Bitartrate Tablets usually available contain the following amounts of choline bitartrate: 500 and 600 mg. I

**CATEGORY and DOSE**—See Choline Bitartrate.

**CHOLINE DIHYDROGEN CITRATE**

(2-Hydroxyethyl)trimethylammonium Citrate



Choline Dihydrogen Citrate contains not less than 98 per cent of  $C_{11}H_{21}NO_8$ , calculated on the anhydrous basis.

**Description**—Choline Dihydrogen Citrate occurs as colorless, translucent crystals, or as a white, granular to fine, crystalline powder. It is odorless or it may have a faint trimethylamine odor. It has an acidic taste. It is hygroscopic.

**Solubility**—One Gm. of Choline Dihydrogen Citrate dissolves in 1 ml. of water and in 42 ml. of alcohol. It is very slightly soluble in ether, in chloroform, and in benzene.

**Identification—**

**A:** Dissolve 500 mg. of Choline Dihydrogen Citrate in 2 ml. of water, add 3 ml. of sodium hydroxide T.S., and heat to boiling: the odor of trimethylamine is detectable.

**B:** Dissolve 500 mg. of Choline Dihydrogen Citrate in 1 ml. of water and add 3 ml. of iodine T.S.: a reddish brown precipitate is immediately formed. Add 5 ml. of sodium hydroxide T.S.: the precipitate dissolves and the solution acquires a clear yellow color. Heat the solution to boiling: a pale yellow precipitate forms and the odor of iodoform may be detected.

Hyd

of Cl  
is not

an estimated concentration of 1 mg. in each ml., a for 5 minutes. Using this as the *Assay* *P.* *ion*, proceed as directed under *Chlortetracycline Microbial Assay*, page 409.

**Packaging and storage**—Preserve Chlortetracycline Hydrochloride Capsules in tight, light-resistant containers.

**Capsules available**—Chlortetracycline Hydrochloride Capsules usually available contain the following amounts of chlortetracycline hydrochloride: 50, 100, and 250 mg.

**CATEGORY and DOSE**—See Chlortetracycline Hydrochloride.

### Chlortetracycline Hydrochloride for Injection

Chlortetracycline Hydrochloride for Injection is a sterile, dry mixture of chlortetracycline hydrochloride with a suitable buffer, the latter usually consisting of an amino acid. It contains not less than 85 per cent of the labeled amount of  $C_{22}H_{23}ClN_7O_8 \cdot HCl$ . Chlortetracycline Hydrochloride for Injection conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

**Identification**—Chlortetracycline Hydrochloride for Injection responds to *Identification tests A and B* under *Chlortetracycline Hydrochloride*, page 85, about twice the quantity of sample therein specified being used.

The pH of a 1 per cent solution of Chlortetracycline Hydrochloride for Injection is between 8.0 and 9.5.

**Loss on drying, Depressor substances, Pyrogen, Safety, and Sterility**—Chlortetracycline Hydrochloride for Injection meets the requirements of the tests for *Loss on drying, Depressor substances, Pyrogen, Safety, and Sterility* under *Chlortetracycline Hydrochloride*, page 85.

**Content variation**—The content in containers of Chlortetracycline Hydrochloride for Injection is not less than 85 per cent of the labeled content as determined by the *Assay*.

**Assay**—Proceed as directed in the *Assay* under *Chlortetracycline Hydrochloride*, page 85, dissolving the sample in water, and diluting immediately.

**Packaging and storage**—Preserve Chlortetracycline Hydrochloride for Injection in single-dose or multiple-dose containers.

**Labeling**—Chlortetracycline Hydrochloride for Injection complies with the requirements of *Labeling* under *Injections*, page 435. The container label indicates the solvent recommended for preparing a solution for injection.

**Sizes available**—Chlortetracycline Hydrochloride for Injection usually available contains the following amounts of chlortetracycline hydrochloride: 100 and 500 mg.

**CATEGORY and DOSE**—See Chlortetracycline Hydrochloride.

### Ophthalmic Chlortetracycline Hydrochloride

Ophthalmic Chlortetracycline Hydrochloride is a sterile, dry mixture of chlortetracycline hydrochloride with a suitable buffer. It contains not less than 85 per cent of the labeled amount of  $C_{22}H_{23}ClN_7O_8 \cdot HCl$ . It may contain suitable bacteriostatic agents and diluents. Ophthalmic Chlortetracycline Hydrochloride conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

**Identification**—Ophthalmic Chlortetracycline Hydrochloride responds to *Identification tests A and B* under *Chlortetracycline Hydrochloride*, page 85, about twice the quantity of sample therein specified being used.

**pH**—The pH of a solution of Ophthalmic Chlortetracycline Hydrochloride containing the equivalent of 1 mg. of chlortetracycline hydrochloride in each ml. is between 7.9 and 8.4.

**Loss on drying**, page 437—Dry about 100 mg. of Ophthalmic Chlortetracycline Hydrochloride, accurately weighed, in vacuum at 60° for 3 hours; it loses not more than 5 per cent of its weight.

**Sterility**—Ophthalmic Chlortetracycline Hydrochloride meets the requirements of the test for *Sterility* under *Chlortetracycline Hydrochloride*, page 85, except that no tube may show growth in either the test for bacteria or mold.

**Assay**—Proceed as directed in the *Assay* under *Chlortetracycline Hydrochloride*, page 85, dissolving the sample in water, and diluting immediately.

**Packaging and storage**—Preserve Ophthalmic Chlortetracycline Hydrochloride in tight containers.

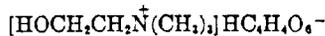
**Sizes available**—Ophthalmic Chlortetracycline Hydrochloride usually available contains the following amount of chlortetracycline hydrochloride: 25 mg. in each vial.

**CATEGORY**—Antibiotic.

**FOR EXTERNAL USE**—Topically in solution to lids or conjunctivas as required.

### CHOLINE BITARTRATE

(2-Hydroxyethyl)trimethylammonium Bitartrate



$C_9H_{19}NO_7$

Mol. wt. 253.26

Choline Bitartrate contains not less than 98 per cent of  $C_9H_{19}NO_7$ , calculated on the anhydrous basis.

**Description**—Choline Bitartrate occurs as a

white, crystalline powder. It is odorless or may have a faint trimethylamine-like odor. It has an acidic taste. It is hygroscopic.

**Solubility**—Choline Bitartrate is freely soluble in water and slightly soluble in alcohol. It is insoluble in ether, in chloroform, and in benzene.

**Identification**—

**A:** Dissolve 500 mg. of Choline Bitartrate in 2 ml. of water, add 3 ml. of sodium hydroxide T.S., and heat to boiling: the odor of trimethylamine is detectable.

**B:** Dissolve 500 mg. of Choline Bitartrate in 2 ml. of iodine T.S.: a reddish brown precipitate is immediately formed. Add 5 ml. of sodium hydroxide T.S.: the precipitate dissolves and the solution becomes a clear yellow. Heat the solution to boiling: a pale yellow precipitate forms and the odor of iodoform may be detected.

**C:** To 2 ml. of cobaltous chloride T.S. add 1 ml. of a solution of Choline Bitartrate (1 in 100) and 2 ml. of potassium ferrocyanide solution (1 in 50): an emerald-green color develops immediately.

**D:** Choline Bitartrate solution responds to the tests for *Tartrate*, page 434.

**Water**, page 467—Determine the water content by drying about 500 mg. of Choline Bitartrate, accurately weighed, in a vacuum desiccator over phosphorus pentoxide for 4 hours or by the titrimetric (Karl Fischer) method, using a 2-Gm. sample dissolved in 50 ml. of anhydrous methanol: it contains not more than 0.5 per cent of water.

**Residue on ignition**, page 448—Choline Bitartrate yields not more than 0.1 per cent of residue on ignition.

**Heavy metals**, page 430—Dissolve 2 Gm. of Choline Bitartrate in 20 ml. of water, add 2 ml. of diluted acetic acid, and dilute to 25 n.l. with water: the heavy metals limit for Choline Bitartrate is 20 parts per million.

**Assay**—Weigh accurately about 100 mg. of Choline Bitartrate. Dissolve it in 40 ml. of water in a 150-ml. beaker, and carefully add 10 ml. of freshly prepared saturated ammonium reineckate solution from a pipet, allowing it to run down the side of the beaker so that it forms a layer under the choline solution without producing turbulence. Mix by rotating the beaker gently and allow to stand in a refrigerator for one hour, rotating the beaker from time to time. Filter, collect the precipitate in a tared 30-ml. low form sintered-glass crucible of medium porosity using gentle suction, and rinse the beaker with three 10-ml. portions of a wash solution prepared by diluting 2 ml. of saturated ammonium reineckate solution to 1000 ml. with water cooled to 5°, and pass these consecutively through the crucible containing the precipitate. Remove as much water as possible with suction, then dry in an oven at 105° for 1 hour. Cool in a desiccator and weigh as choline reineckate. The weight of the choline reineckate multiplied by 0.5993 gives the equivalent weight of  $C_9H_{19}NO_7$ .

**Packaging and storage**—Preserve Choline Bitartrate in tight containers.

**CATEGORY**—Lipotropic.

**USUAL DOSE**—2 Gm.

Database: Medline &lt;1966 to present&gt;

| Set | Search                 | Results |
|-----|------------------------|---------|
| 1   | exp choline/           | 23968   |
| 2   | choline bitartrate.tw. | 9       |
| 3   | from 2 keep 2,4,6,8    | 4       |

&lt;1&gt;

Unique Identifier

97028826

Authors

Stoll AL. Sachs GS. Cohen BM. Lafer B. Christensen JD.  
Renshaw PF.

Title

Choline in the treatment of rapid-cycling bipolar disorder:  
clinical and neurochemical findings in lithium-treated  
patients.

Source

Biological Psychiatry. 40(5):382-8, 1996 Sep 1.

Abstract

This study examined choline augmentation of lithium for rapid-cycling bipolar disorder. Choline bitartrate was given openly to 6 consecutive lithium-treated outpatients with rapid-cycling bipolar disorder. Five patients also underwent brain proton magnetic resonance spectroscopy. Five of 6 rapid-cycling patients had a substantial reduction in manic symptoms, and 4 patients had a marked reduction in all mood symptoms during choline therapy. The patients who responded to choline all exhibited a substantial rise in the basal ganglia concentration of choline-containing compounds. Choline was well tolerated in all cases. Choline, in the presence of lithium, was a safe and effective treatment for 4 of 6 rapid-cycling patients in our series. A hypothesis is suggested to explain both lithium refractoriness in patients with bipolar disorder and the action of choline in mania, which involves the interaction between phosphatidylinositol and phosphatidylcholine second-messenger systems.

&lt;2&gt;

Unique Identifier

95405204

Authors

Spector SA. Jackman MR. Sabounjian LA. Sakkas C.

Landers DM. Willis WT.

Title

Effect of choline supplementation on fatigue in trained cyclists.

Source

Medicine & Science in Sports & Exercise. 27(5):668-73, 1995 May.

Abstract

The availability of choline, the precursor of the neurotransmitter, acetylcholine, in the diet is sufficient to provide the body's requirements under normal conditions. However, preliminary evidence indicates that depletion of choline may limit performance, while oral supplementation may delay fatigue during prolonged efforts. A double-blind cross-over design was used to determine the relationship between plasma choline and fatigue during supramaximal brief and submaximal prolonged activities. Twenty male cyclists (ages 23-29) with maximal aerobic power (VO<sub>2</sub>max) between 58 and 81 ml.min<sup>-1</sup>.kg<sup>-1</sup> were randomly divided into BRIEF (N = 10) and PROLONGED (N = 10) groups. One hour after drinking a beverage with or without choline bitartrate (2.43 g), cyclists began riding at a power output equivalent to approximately 150% (BRIEF) and 70% (PROLONGED) of VO<sub>2</sub>max at a cadence of 80-90 rpm. Time to exhaustion, indirect calorimetry and serum choline, lactate, and glucose were measured. Increases in choline levels of 37 and 52% were seen within one hour of ingestion for BRIEF and PROLONGED groups, respectively. Neither group depleted choline during exercise under the choline or placebo conditions. Fatigue times and work performed under either test condition for the BRIEF or PROLONGED groups were similar. Consequently, trained cyclists do not deplete choline during supramaximal brief or prolonged submaximal exercise, nor do they benefit from choline supplementation to delay fatigue under these conditions.

<3>

Unique Identifier

81043075

Authors

Fovall P. Dysken MW. Lazarus LW. Davis JM. Kahn RL. Jope R. Finkel S. Rattan P.

Title

Choline bitartrate treatment of Alzheimer-type dementias.

Source

Communications in Psychopharmacology. 4(2):141-5, 1980.

G\*

<4>

Unique Identifier

68236336

Authors

Beauregard WG.

Title

G \* Dexpanthenol with choline bitartrate in the treatment of  
infantile colic.

Source

Journal of the Louisiana State Medical Society.

120(3):142-5, 1968 Mar.

# Dexpanthenol with Choline Bitartrate in the Treatment of Infantile Colic

Reprinted with permission  
through the Copyright  
Clearance Center

● Fifty infants with colic were treated with Ilopan® Choline-WT. Excellent response was achieved in 72 per cent and there were few side effects.

W. G. BEAUREGARD, MD\*  
West Monroe

THE problem of infantile colic is familiar to any physician who cares for babies. Although only light mention is made of this problem in most pediatric literature, the situation can be very disturbing to both the attending physician and to the parents. A recent discussion<sup>1</sup> on this topic emphasized that much crying which is called colic is actually normal crying which the parents should learn to accept. Many parents commonly mistake the two to six hour daily restless period for colic. This "activity period" or "exercise period" often occurs at the same time each day, usually in the late afternoon or early at night. It is the physician's duty to inform the inexperienced parents of this normal restlessness and to explain that some babies simply cry more than others.<sup>4,5</sup> The laity has unduly labeled many forms of infantile restlessness as "the colic", and each case must be individually evaluated to determine whether or not "true colic" does exist.

## The Colic Syndrome

The syndrome which is usually called "colic" is characterized by prolonged high-pitched screaming associated with alternate forceful flexion and extension of the thighs. The hands are tightly clenched, and on examining these babies one notices a generalized hypertonus of the musculature, or "tension". Breath-holding is not unusual and is often associated with a transient dusky hue of the skin. The eyes are firmly closed, and the forehead is contracted into a frown. The abdomen is

\* Reprint requests to 1607 N. Seventh St., West Monroe, La.

often tight to palpation. There is often a family history of similar hyperirritability during the newborn period of either or both parents. Occasionally, the examiner will detect signs or symptoms of tension in the parents.

## Symptom Complex Subsides in Three Months

The passage of excessive flatus during these episodes is not uncommon; many of these infants are slow to burp or cannot be burped at all. Aerophagia, associated with a marked desire to suck and a voracious appetite, is commonly observed. Sometimes air-swallowing can be heard during feedings. The increased motor activity with a marked sucking reflex may give the impression that the baby interprets his colic pains as hunger pains; this causes more aerophagia with each feeding which results in more colic. Fortunately, this symptom complex usually has subsided by the age of 3 months.<sup>6</sup>

## Aerophagic Colic

The infant under consideration in this study is the one whose colic seems to stem mainly from aerophagia. He may be difficult to burp after feedings, and he may temporarily be unable to pass enough flatus to relieve abdominal distention. Changing nipples, bottles and formulas may offer very little improvement. His rapid intake of formula allows considerable air to be swallowed, regardless of the feeding system used.

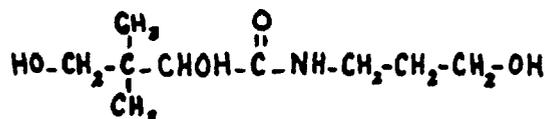
## Antispasmodic Drugs Traditional

Traditionally, antispasmodic drugs have been the cardinal treatment for colic. In

many instances relief or partial relief is afforded by atropine or belladonna derivatives such as dicyclomine hydrochloride, meclizine hydrochloride, hyoscine hydrobromide and others either alone or in combination with barbiturates or other sedatives. Because these agents are often disappointing in relieving colic due to aerophagia, this study was undertaken to evaluate the converse therapeutic approach—that of using an agent which increases intestinal motility rather than one which diminishes it.

### Pharmacology

Dexpanthenol (Dextro-pantothenyl alcohol) is the alcohol analogue of d-pantothenic acid, a member of the B-complex group of vitamins:



(DEXTRO PANTOTHENYL ALCOHOL)

Fig 1.

On the basis of theoretical considerations, dexpanthenol has been used for the prevention and therapy of gastrointestinal atony or distention. The rationale for the use of dexpanthenol is based on the assumption that its administration increases the amount of coenzyme A available for the formation of acetylcholine, which, in turn, increases intestinal tone. So far, no one has conclusively demonstrated that the administration of dexpanthenol will lead to an increase in coenzyme A and acetylcholine; thus, the scientific basis for the use of dexpanthenol has not yet been proved. However, many clinical observers are convinced that it does increase intestinal motility.

Choline is the parent substance of acetylcholine, a neurohumoral substance required for gastrointestinal tonus and peristaltic efficiency.

### Side Effects

No untoward effects have been reported with the use of dexpanthenol even when large doses were administered; thus the agent appears to be relatively nontoxic.

The only known contraindication to the use of dexpanthenol is hemophilia, in which it may have a tendency to prolong bleeding time. Theoretical considerations suggest that dexpanthenol should not be used for at least 12 hours after parasympathomimetic drugs have been administered. Respiratory embarrassment was observed in one case report when dexpanthenol was administered shortly after succinylcholine therapy.

The only side effects observed during this study were an occasional increase in frequency of defecation and in three cases, some mild diarrhea which subsided when the drug was withdrawn (Table 1).

TABLE 1

| Side Effects   | Number of Cases | Percentage |
|----------------|-----------------|------------|
| Mild Diarrhea: | 3               | 6          |

### Method

Fifty infants were individually evaluated at various times during their first 3 months of life. All colic was considered to be related to aerophagia, increased sucking activity, and an unusually voracious appetite with rapid intake of feedings. The parents were questioned closely regarding feeding habits, feeding techniques, variety of foods, family history of colic and the general and specific behavior of the infants before, during and after feedings. Cases in which colic was not thought to be due to aerophagia were excluded from the study group. In all instances the parents affirmed that smacking noises or air swallowing could be heard during feedings. Very often, colic was noted soon after feedings and was associated with increased expulsion of flatus.

Each infant had previously been treated with an antispasmodic-sedative combination in the usual therapeutic amounts with only partial or no improvement in symptoms. The drugs initially used were either methscopolamine bromide, dicyclomine hydrochloride, meclizine hydrochloride, or hyoscine hydrobromide (each combined with phenobarbital). In some cases refractive to these drugs other antispasmodic-sedative combinations were used

unsuccessfully. Usually, this was done when a hyperirritability reaction due to the phenobarbital was suspected.

When symptoms and signs did not disappear with the original therapy, the infants were placed on dexpanthenol with choline bitartrate (Ilopan® Choline-WT) alone. Because this product is presently available only in tablet form, the drug was crushed and mixed in Serpalta or raspberry syrup so that one teaspoonful of syrup was the equivalent of one tablet (50 mgm Ilopan and 25 mgm choline bitartrate). Refrigeration was recommended in order to prevent overgrowth of mold or other contaminants. The dosage for all infants was one teaspoonful (one tablet) every eight hours.

Parents were asked to report on the effectiveness of the drug four to five days after beginning therapy. They were specifically asked to watch for:

- 1) Any improvement of signs and symptoms of colic—especially less crying, less restlessness, less abdominal distention.
- 2) Increased expulsion of flatus.
- 3) Side effects—especially increased frequency or loosening of stools.

#### Comment

This study was undertaken to evaluate the effectiveness of a drug which increases intestinal motility in relieving infantile colic due to retained gas and swallowed air. Admittedly, this report is highly subjective, depending greatly on the opinions of the parents so that "outside factors" must be considered. The parents, for example, might conceivably have been more relaxed because they were using a medication which they felt would solve the problem. This lessening of anxiety could have created a more relaxed environment for the infant and possibly improved his colic. Of some significance, however, is the fact that all infants had been previously treated with at least one of several antispasmodic-sedative combinations with only partial or no relief of colic symptoms.

Most of the infants were treated in the first month of life but an occasional case

was first evaluated during the second month. Since colic is a temporary condition, there is always the possibility that improvement occurred spontaneously.

Fifty colicky infants were treated and observed mainly to determine whether any relief could be obtained after an unsatisfactory response to antispasmodic therapy. This is not to suggest that antispasmodic-sedative combinations are usually inadequate; to the contrary, many cases of colic are afforded much relief by the usual agents. There are some affected infants, however, who seem to obtain relief mainly by expulsion of flatus with increased bowel tone. That 72 per cent of infants in this group showed improvement suggests that carefully controlled studies on a large scale might be worthwhile.

#### Results

Since this was not a "double-blind study", the subjective data obtained from the parents were compiled and arranged in three very general categories: excellent, fair, and poor (Table 2).

TABLE 2

| Categories | Number of Cases | Percentage |
|------------|-----------------|------------|
| Excellent  | 36              | 72         |
| Fair       | 11              | 22         |
| Poor       | 3               | 6          |
| Total:     | 50              | 100        |

An "excellent" response was considered one in which marked improvement in crying, restlessness, abdominal distention, and expulsion of flatus afforded complete or near complete relief of colic with only occasional recurrent episodes noted.

A "fair" response was one in which restlessness and crying showed slight or temporary improvement, although increased frequency and amount of flatus were obvious.

The "poor" category included the cases in which the parents were able to observe no improvement of any type.

Colic is a troublesome syndrome but it cannot be considered as dangerous to the infant. For this reason any therapeutic approach must be reasonably safe with no serious side effects. The excellent safety

## TREATMENT OF INFANTILE COLIC—BEAUREGARD

record of dexpanthenol-choline would lend support to its use in infants with aerophagia and colic. Should further studies confirm its efficacy, another advantage would be the prospect of relatively prolonged therapy with no likelihood of addiction.

### Summary

Fifty infants with colic apparently related to aerophagia and retained intestinal gas were treated with three daily doses of dexpanthenol-choline. All cases had responded poorly to antispasmodic-sedative combinations.

Thirty-six of 50 (72%) infants had an excellent response to treatment with less crying, less restlessness, and more expulsion of flatus.

No serious side effects were noted.

It is hoped that further experience with dexpanthenol-choline in the treatment of

aerophagia and colic in infants may confirm the safety and effectiveness of this drug.

### Acknowledgment

I wish to thank Dr. Paul F. Geiger and Dr. T. H. Eickholt of the Northeast Louisiana State College of Pharmacy for their assistance.

### References

1. Hill, Lee Forrest: *Infant Feeding: Historical and Current*, *Pediat Clin N Amer* 14:263-265, 1967.
2. Wessel, Morris A.; Cobb, John C.; Jackson, Edith B.; Harris, George S., Jr.; and Detwiler, Ann C.: Paroxysmal Fussing in Infancy, Sometimes Called "Colic", *Pediatrics* 14:421-433, 1954.
3. Holt, Emmett L. Jr.; McIntosh, Rustin; and Barnett, Henry L.: *Pediatrics*, New York: Appleton-Century-Crofts, Inc., pp 260-261, 1962.
4. Rambar, A. C.: Colic in Infants—General Considerations, *Pediatrics* 18:829, 1956.
5. Aldrich, C. A.; Sung, C.; and Knop, C.: The Crying of Newly Born Babies. III. The Early Period at Home, *J Pediat* 27:428, 1945.
6. Schaffer, Alexander J.: *Diseases of the Newborn*, ed 2, Philadelphia and London: W. B. Saunders Co., p 785, 1965.

### Consultant Post

"Dr. Irving M. Blatt of New Orleans has been appointed a national consultant in Otolaryngology to the Surgeon General, United States Air Force. Dr. Blatt is professor and head of the Department of Otorhinolaryngology, Louisiana State University School of Medicine, New Orleans. *Times Picayune* (Mar 7) 1968.

Reprinted with permission  
through the Copyright  
Clearance Center

Communications in Psychopharmacology, Vol. 4, pp. 141-145 (1980)  
Printed in the U.S.A. All rights reserved.

0145-5699/80/020141-05\$02.00/0  
Copyright (c) 1980 Pergamon Press Ltd

NOTICE  
THIS MATERIAL MAY BE PROTECTED BY  
COPYRIGHT LAW (TITLE 17, U.S. CODE)

#### CHOLINE BITARTRATE TREATMENT OF ALZHEIMER-TYPE DEMENTIAS

Penny Fovall, Maurice W. Dysken, Lawrence W. Lazarus,  
John M. Davis, Robert L. Kahn, Richard Jope,  
Sanford Finkel, Pradeep Rattan  
Research Department  
Illinois State Psychiatric Institute  
Chicago, Illinois 60612  
and  
Department of Psychiatry  
University of Chicago Pritzker School of Medicine  
Chicago, Illinois 60637  
and  
Department of Pharmacology  
UCLA School of Medicine  
Los Angeles, California 90024

#### Abstract

We conducted a double-blind, placebo controlled study of the effects of choline bitartrate on intellectual performance in 5 patients with early Alzheimer-type dementia. Three doses of choline bitartrate (8 gm, 12 gm, and 16 gm) were given for two weeks each with a two-week placebo period either preceding (N=2) or following (N=3) the drug period. Cognitive testing was administered during a baseline period and thereafter once a week for the duration of the study. Comparing drug condition with placebo, we found significant improvement for auditory and visual word recognition at 12 gm per day of choline bitartrate. The mean plasma choline level nearly doubled from baseline to 12 gm per day. These results suggest improvement in some aspects of cognitive performance during choline bitartrate treatment.

#### Introduction

This paper reports the effects of choline bitartrate on cognitive functioning in early Alzheimer's disease and senile dementia of the Alzheimer type. The impetus for this study came from preliminary neurochemical reports suggesting that choline acetyltransferase (C.A.T.) activity, a possible marker of presynaptic cholinergic neurons, is substantially reduced in areas of cerebral cortex in Alzheimer's disease relative to that of normal age matched controls (3-5). Preliminary studies have raised the possibility that muscarinic acetylcholine receptors are still intact (3-5). This suggests that Alzheimer's disease might involve a selective impairment of the presynaptic cholinergic system (3). Choline treatment, which raises brain acetylcholine, might restore the hypothesized decrement

in central acetylcholine. If so, this restoration could lead to an improvement in cognitive functioning.

Pilot studies of the effect of choline on cognitive performance and on observer-rated behavior have yielded mixed results. Patients were less irritable and more alert (6), but some experienced exacerbated urinary incontinence (7) and depression (8). In one open study of choline chloride, some patients had improved behavior ratings (6) (2 weeks each of 5 and 10 gm daily), but in a more extensive placebo controlled trial (2 months of 15 gm daily), others showed no improvement (9). A controlled study of the effects of choline chloride (16 gm daily for 1 week) on healthy elderly people with mild to moderate memory problems failed to demonstrate effects on memory, mood or overall social functioning (10). In another open study, patients with early Alzheimer-type dementia who received choline citrate (3 weeks of 9 gm daily) showed some improvement in cognitive performance (11). Two placebo controlled trials of choline bitartrate (4 weeks of up to 10 gm daily; and 2 weeks of 9 gm daily) did not produce any improvement in cognitive performance or behavior ratings, although some patients displayed less confusion (7,8,9). Given these mixed yet suggestive findings, we decided to test the effects of choline bitartrate in a double-blind, placebo-controlled study. Three different doses were given in an attempt to identify a dose which might produce a therapeutic effect. Mildly to moderately impaired Alzheimer outpatients were carefully selected because treatment might be most effective in patients whose cholinergic neurons were only mildly affected.

#### Materials and Methods

The patients, three men and two women (55-77 years,  $M = 69.8$ ;  $S.D. = 6.7$ ), were referred to us after medical and neurologic evaluations for dementia. Diagnostic studies including skull films, EEG, and CAT scan were obtained and were consistent with the presence of Alzheimer's disease (12). Of the 12 patients evaluated for treatment during the two months before the study began, six met the selection criteria. However, one was dropped from the study because she became anxious, developed a foul fishy odor, and experienced nausea and belching during the 8 gm trial. Each patient plus a family member gave written informed consent.

The cognitive test battery consisted of ten tasks. Four memory tasks involved immediate recall of a logical paragraph (13), logical sentences (13), meaningless sentences (13), and geometric figures (Benton Revised Visual Retention Test, Form C) (14). Two other memory tasks assessed immediate recognition of word lists presented auditorily and visually (13). The Face-Hand-Test (FHT) (15,16) and the Mental Status Questionnaire (MSQ) (15,16) served as clinical measures for the assessment of altered brain function. The digit symbol (17) was used to test psychomotor speed and a Control Rating Scale (13) was included to assess a subjective sense of control. Behavioral evaluations by a family member were obtained by completion of the Sandoz Clinical Assessment-Geriatric (SCAG) (18). These 11

tests yielded 13 scores: the Benton was scored for number of errors and correct reproductions. SCAG items 1 through 18 were totaled and examined separately from the 19th item, scored for overall impression of the patient. The choline and placebo were administered in tablet form and were identical in appearance (Nature's Bounty, Inc., Bohemia, N.Y.).

Each patient was pretested three times at 48 hour intervals. There was variability in performance but no observable learning or practice effects. Random assignment of patients was made to one of two treatment sequences: (1) two weeks each of baseline, 1st placebo, 8 gm choline, 12 gm choline, 16 gm choline and 1 week of 2nd placebo (N=3); (2) two weeks each of baseline, 8 gm choline, 12 gm choline, 16 gm choline, 1st placebo and 1 week of 2nd placebo (N=2). At the end of each treatment week patients were tested, SCAG ratings were obtained, and a 10 ml blood sample was drawn for plasma choline determination (19).

For each patient, scores were averaged for each treatment to yield one score per treatment per patient. The two treatment sequences were combined for statistical analysis. There were no significant differences between the 1st and 2nd placebo scores, hence they were combined. The 13 scores were subjected to statistical analysis by means of a mixed model analysis of variance for repeated measures (20).

### Results

A main effect for drug condition (8 gm, 12 gm, 16 gm) versus placebo condition was examined as shown in TABLE I. Post-hoc comparisons were made if the analysis yielded any significant or nearly significant results. A drug main effect was found for the visual presentation word recognition task ( $F = 3.4$ ;  $df = 3.25$ ;  $p < 0.05$ ) but did not reach statistical significance for the auditory presentation word recognition task ( $F = 1.1$ ;  $df = 3.25$ ;  $p = 0.37$ ) because of large within-subjects variability. Post-hoc comparisons revealed that patients recognized more words during the 12 gm than during the placebo condition for both visual ( $t = 2.7$ ;  $df = 24$ ;  $p < 0.02$ ) and auditory presentations ( $t = 2.1$ ;  $df = 24$ ;  $p < 0.03$ ). Plasma choline levels rose from a mean ( $\pm$ S.E.M.) of  $3.9 \pm 0.5$  nM/ml during the baseline-placebo period to  $7.2 \pm 1.3$  nM/ml during the 12 gm per day period ( $t = 2.47$ ;  $df = 7$ ;  $p < 0.03$ ).

### Discussion

The purpose of this pilot study in a carefully selected group of mildly impaired outpatients with Alzheimer-type dementia was to find a dose of choline bitartrate that might produce a therapeutic effect and to discover which cognitive tests would be most sensitive to a change in intellectual performance. At 12 gm per day of choline bitartrate we found enhanced performance on the word recognition tasks. At this

TABLE I  
Association of Choline Dose with Cognitive and Behavioral Scores

| Drug Condition | Dependent Measures                                    |   |
|----------------|---|---|
|                | Word Recognition<br>Auditory Presentation<br>(M ± SD) | Word Recognition<br>Visual Presentation<br>(M ± SD) |
| Baseline       | 6.3 ± 3.8   | 5.0 ± 2.8   |
| Placebo*       | 7.3 ± 3.9   | 4.5 ± 2.0   |
| 8 gm           | 7.6 ± 3.4   | 5.4 ± 2.5   |
| 12 gm          | 8.7 ± 3.9**   | 6.5 ± 2.8***  |
| 16 gm          | 8.0 ± 3.2   | 4.5 ± 2.6   |

\*Placebo scores were combined for statistical analysis but were obtained both before and after drug treatment

\*\*F = 1.1; df = 3,25; p = 0.37

\*\*\*F = 3.4; df = 3,25; p < 0.05

dose of choline the mean plasma choline level was nearly double the mean value during the baseline-placebo period.

Since lecithin, the principal source of choline in the diet, does not produce the fishy odor that choline sometimes does, we have discontinued choline bitartrate administration in favor of lecithin. Although we would not normally report work on such a small sample of patients, we feel that doing so is warranted as a preliminary attempt in identifying an effective choline dose and plasma level. In evaluating any new pharmacological agent, it is important to avoid premature negative results due to inappropriate selection of patients, inadequate dose, or insensitive measures of clinical response. For this reason a dose ranging pilot study that finds a dose related therapeutic effect can be a useful guide for more extensive studies in the future.

#### Acknowledgements

This work was supported in part by USPHS MH-17691 and by the Department of Mental Health, State of Illinois.

#### References

1. White, P., Hiley, C.R., Goodhardt, M.J., Carrasco, L.H., Keet, J.P., Williams, I.E.I. and Bowen, D.M., *Lancet* 1, 668-670 (1977).
2. Davies, P. and Maloney, A.J.F., *Lancet* 2, 1403 (1976).
3. Davies, P., in press.
4. Spillane, J.A., Goodhardt, M.J., White, P., Bowen, D.M. and Davison, A.N., *Lancet* 2, 826-827 (1977).

5. Perry, E.K., Perry, R.H., Blessed, G. and Tomlinson, B.E., *Lancet* 1, 189 (1977).
6. Boyd, W.D., Graham-White, J., Blackwood, G., Glen, T. and McQueen, J., *Lancet* 2, 711 (1977).
7. Etienne, P., Gauthier, S., Johnson, G., Collier, B., Mendis, T., Dastoor, D., Cole, M. and Muller, H.F., *Lancet* 1, 508-509 (1978).
8. Smith, C.M., Swash, M., Exton-Smith, A.N., Phillips, M.J., Overstall, P.W., Piper, M.E. and Bailey, M.R., *Lancet* 2, 318 (1978).
9. Renvoize, E.B., Jerram, T., *NEJM* 301, 330 (1979).
10. Mohs, R.C., Davis, K.L., Tinklenberg, J.R., Hollister, L.E., Yesavage, J.A. and Kopell, B.S., *Am J Psychiatry* 136, 1275-1277 (1979).
11. Signoret, J.L., Whiteley, A. and Lhermittee, P., *Lancet* 2, 837 (1978).
12. Wells, C.E., *Am J Psychiatry* 135, 1-12 (1978).
13. Botwinick, J. and Storandt, M., *Memory, Related Functions and Age*, Springfield: Charles C. Thomas, 1974.  
Benton, A.L., *Revised Visual Retention Test: Clinical and Experimental Applications*, Fourth Edition, New York: The Psychological Corporation, 1974.
15. Kahn, R.L. and Miller, N., in *The Clinical Psychology of Aging*, edited by M. Storandt, I.C. Seigler, and M.F. Elias, pp. 43. New York: Plenum Press (1978).
16. Kahn, R.L., Goldfarb, A.I., Pollack, M. and Peck, A., *Am J Psychiatry* 117, 326-328 (1960).
17. Wechsler, D., *The Measurement of Adult Intelligence*, Third Edition, Baltimore: Williams and Wilkins Company, 1944.
18. Shader, R.I., Harmatz, J.S., Salzman, C., *J Am Geriatr Soc* 22, 107-113 (1974).
19. Jender, D.J., Roch, M. and Booth, R.A., *Anal Biochem* 55, 438-448 (1973).
20. Bock, R.D., *Multivariate Statistical Methods in Behavioral Research*, USA: McGraw-Hill, Inc., 1975.

Reprinted with permission  
through the Copyright  
Clearance Center

*Communications in Psychopharmacology*, Vol. 4, pp. 141-145 (1980)  
Printed in the U.S.A. All rights reserved.

0145-5699/80/020141-05\$02.00/0  
Copyright (c) 1980 Pergamon Press Ltd

NOTICE  
THIS MATERIAL MAY BE PROTECTED BY  
COPYRIGHT LAW (TITLE 17, U.S. CODE)

#### CHOLINE BITARTRATE TREATMENT OF ALZHEIMER-TYPE DEMENTIAS

Penny Fovall, Maurice W. Dysken, Lawrence W. Lazarus,  
John M. Davis, Robert L. Kahn, Richard Jope,  
Sanford Finkel, Pradeep Rattan  
Research Department  
Illinois State Psychiatric Institute  
Chicago, Illinois 60612  
and  
Department of Psychiatry  
University of Chicago Pritzker School of Medicine  
Chicago, Illinois 60637  
and  
Department of Pharmacology  
UCLA School of Medicine  
Los Angeles, California 90024

#### Abstract

We conducted a double-blind, placebo controlled study of the effects of choline bitartrate on intellectual performance in 5 patients with early Alzheimer-type dementia. Three doses of choline bitartrate (8 gm, 12 gm, and 16 gm) were given for two weeks each with a two-week placebo period either preceding (N=2) or following (N=3) the drug period. Cognitive testing was administered during a baseline period and thereafter once a week for the duration of the study. Comparing drug condition with placebo, we found significant improvement for auditory and visual word recognition at 12 gm per day of choline bitartrate. The mean plasma choline level nearly doubled from baseline to 12 gm per day. These results suggest improvement in some aspects of cognitive performance during choline bitartrate treatment.

#### Introduction

This paper reports the effects of choline bitartrate on cognitive functioning in early Alzheimer's disease and senile dementia of the Alzheimer type. The impetus for this study came from preliminary neurochemical reports suggesting that choline acetyltransferase (C.A.T.) activity, a possible marker of presynaptic cholinergic neurons, is substantially reduced in areas of cerebral cortex in Alzheimer's disease relative to that of normal age matched controls (3-5). Preliminary studies have raised the possibility that muscarinic acetylcholine receptors are still intact (3-5). This suggests that Alzheimer's disease might involve a selective impairment of the presynaptic cholinergic system (3). Choline treatment, which raises brain acetylcholine, might restore the hypothesized decrement

in central acetylcholine. If so, this restoration could lead to an improvement in cognitive functioning.

Pilot studies of the effect of choline on cognitive performance and on observer-rated behavior have yielded mixed results. Patients were less irritable and more alert (6), but some experienced exacerbated urinary incontinence (7) and depression (8). In one open study of choline chloride, some patients had improved behavior ratings (6) (2 weeks each of 5 and 10 gm daily), but in a more extensive placebo controlled trial (2 months of 15 gm daily), others showed no improvement (9). A controlled study of the effects of choline chloride (16 gm daily for 1 week) on healthy elderly people with mild to moderate memory problems failed to demonstrate effects on memory, mood or overall social functioning (10). In another open study, patients with early Alzheimer-type dementia who received choline citrate (3 weeks of 9 gm daily) showed some improvement in cognitive performance (11). Two placebo controlled trials of choline bitartrate (4 weeks of up to 10 gm daily; and 2 weeks of 9 gm daily) did not produce any improvement in cognitive performance or behavior ratings, although some patients displayed less confusion (7,8,9). Given these mixed yet suggestive findings, we decided to test the effects of choline bitartrate in a double-blind, placebo-controlled study. Three different doses were given in an attempt to identify a dose which might produce a therapeutic effect. Mildly to moderately impaired Alzheimer outpatients were carefully selected because treatment might be most effective in patients whose cholinergic neurons were only mildly affected.

#### Materials and Methods

The patients, three men and two women (55-77 years,  $M = 69.8$ ;  $S.D. = 6.7$ ), were referred to us after medical and neurologic evaluations for dementia. Diagnostic studies including skull films, EEG, and CAT scan were obtained and were consistent with the presence of Alzheimer's disease (12). Of the 12 patients evaluated for treatment during the two months before the study began, six met the selection criteria. However, one was dropped from the study because she became anxious, developed a foul fishy odor, and experienced nausea and belching during the 8 gm trial. Each patient plus a family member gave written informed consent.

The cognitive test battery consisted of ten tasks. Four memory tasks involved immediate recall of a logical paragraph (13), logical sentences (13), meaningless sentences (13), and geometric figures (Benton Revised Visual Retention Test, Form C) (14). Two other memory tasks assessed immediate recognition of word lists presented auditorily and visually (13). The Face-Hand-Test (FHT) (15,16) and the Mental Status Questionnaire (MSQ) (15,16) served as clinical measures for the assessment of altered brain function. The digit symbol (17) was used to test psychomotor speed and a Control Rating Scale (13) was included to assess a subjective sense of control. Behavioral evaluations by a family member were obtained by completion of the Sandoz Clinical Assessment-Geriatric (SCAG) (18). These 11

tests yielded 13 scores: the Benton was scored for number of errors and correct reproductions. SCAG items 1 through 18 were totaled and examined separately from the 19th item, scored for overall impression of the patient. The choline and placebo were administered in tablet form and were identical in appearance (Nature's Bounty, Inc., Bohemia, N.Y.).

Each patient was pretested three times at 48 hour intervals. There was variability in performance but no observable learning or practice effects. Random assignment of patients was made to one of two treatment sequences: (1) two weeks each of baseline, 1st placebo, 8 gm choline, 12 gm choline, 16 gm choline and 1 week of 2nd placebo (N=3); (2) two weeks each of baseline, 8 gm choline, 12 gm choline, 16 gm choline, 1st placebo and 1 week of 2nd placebo (N=2). At the end of each treatment week patients were tested, SCAG ratings were obtained, and a 10 ml blood sample was drawn for plasma choline determination (19).

For each patient, scores were averaged for each treatment to yield one score per treatment per patient. The two treatment sequences were combined for statistical analysis. There were no significant differences between the 1st and 2nd placebo scores, hence they were combined. The 13 scores were subjected to statistical analysis by means of a mixed model analysis of variance for repeated measures (20).

### Results

A main effect for drug condition (8 gm, 12 gm, 16 gm) versus placebo condition was examined as shown in TABLE I. Post-hoc comparisons were made if the analysis yielded any significant or nearly significant results. A drug main effect was found for the visual presentation word recognition task ( $F = 3.4$ ;  $df = 3.25$ ;  $p < 0.05$ ) but did not reach statistical significance for the auditory presentation word recognition task ( $F = 1.1$ ;  $df = 3.25$ ;  $p = 0.37$ ) because of large within-subjects variability. Post-hoc comparisons revealed that patients recognized more words during the 12 gm than during the placebo condition for both visual ( $t = 2.7$ ;  $df = 24$ ;  $p < 0.02$ ) and auditory presentations ( $t = 2.1$ ;  $df = 24$ ;  $p < 0.03$ ). Plasma choline levels rose from a mean ( $\pm$ S.E.M.) of  $3.9 \pm 0.5$  nM/ml during the baseline-placebo period to  $7.2 \pm 1.3$  nM/ml during the 12 gm per day period ( $t = 2.47$ ;  $df = 7$ ;  $p < 0.03$ ).

### Discussion

The purpose of this pilot study in a carefully selected group of mildly impaired outpatients with Alzheimer-type dementia was to find a dose of choline bitartrate that might produce a therapeutic effect and to discover which cognitive tests would be most sensitive to a change in intellectual performance. At 12 gm per day of choline bitartrate we found enhanced performance on the word recognition tasks. At this

TABLE I  
Association of Choline Dose with Cognitive and Behavioral Scores

| Drug Condition | Dependent Measures                                    |   |
|----------------|---|---|
|                | Word Recognition<br>Auditory Presentation<br>(M ± SD) | Word Recognition<br>Visual Presentation<br>(M ± SD) |
| Baseline       | 6.3 ± 3.8   | 5.0 ± 2.8   |
| Placebo*       | 7.3 ± 3.9   | 4.5 ± 2.0   |
| 8 gm           | 7.6 ± 3.4   | 5.4 ± 2.5   |
| 12 gm          | 8.7 ± 3.9**   | 6.5 ± 2.8***  |
| 16 gm          | 8.0 ± 3.2   | 4.5 ± 2.6   |

\*Placebo scores were combined for statistical analysis but were obtained both before and after drug treatment

\*\*F = 1.1; df = 3,25; p = 0.37

\*\*\*F = 3.4; df = 3,25; p < 0.05

-----  
dose of choline the mean plasma choline level was nearly double the mean value during the baseline-placebo period.

Since lecithin, the principal source of choline in the diet, does not produce the fishy odor that choline sometimes does, we have discontinued choline bitartrate administration in favor of lecithin. Although we would not normally report work on such a small sample of patients, we feel that doing so is warranted as a preliminary attempt in identifying an effective choline dose and plasma level. In evaluating any new pharmacological agent, it is important to avoid premature negative results due to inappropriate selection of patients, inadequate dose, or insensitive measures of clinical response. For this reason a dose ranging pilot study that finds a dose related therapeutic effect can be a useful guide for more extensive studies in the future.

#### Acknowledgements

This work was supported in part by USPHS MH-17691 and by the Department of Mental Health, State of Illinois.

#### References

1. White, P., Hiley, C.R., Goodhardt, M.J., Carrasco, L.H., Keet, J.P., Williams, I.E.I. and Bowen, D.M., *Lancet* 1, 668-670 (1977).
2. Davies, P. and Maloney, A.J.F., *Lancet* 2, 1403 (1976).
3. Davies, P., in press.
4. Spillane, J.A., Goodhardt, M.J., White, P., Bowen, D.M. and Davison, A.N., *Lancet* 2, 826-827 (1977).

5. Perry, E.K., Perry, R.H., Blessed, G. and Tomlinson, B.E., *Lancet* 1, 189 (1977).
6. Boyd, W.D., Graham-White, J., Blackwood, G., Glen, T. and McQueen, J., *Lancet* 2, 711 (1977).
7. Etienne, P., Gauthier, S., Johnson, G., Collier, B., Mendis, T., Dastoor, D., Cole, M. and Muller, H.F., *Lancet* 1, 508-509 (1978).
8. Smith, C.M., Swash, M., Exton-Smith, A.N., Phillips, M.J., Overstall, P.W., Piper, M.E. and Bailey, M.R., *Lancet* 2, 318 (1978).
9. Renvoize, E.B., Jerram, T., *NEJM* 301, 330 (1979).
10. Mohs, R.C., Davis, K.L., Tinklenberg, J.R., Hollister, L.E., Yesavage, J.A. and Kopell, B.S., *Am J Psychiatry* 136, 1275-1277 (1979).
11. Signoret, J.L., Whiteley, A. and Lhermittee, P., *Lancet* 2, 837 (1978).
12. Wells, C.E., *Am J Psychiatry* 135, 1-12 (1978).
13. Botwinick, J. and Storandt, M., *Memory, Related Functions and Age*, Springfield: Charles C. Thomas, 1974.
14. Benton, A.L., *Revised Visual Retention Test: Clinical and Experimental Applications*, Fourth Edition, New York: The Psychological Corporation, 1974.
15. Kahn, R.L. and Miller, N., in *The Clinical Psychology of Aging*, edited by M. Storandt, I.C. Seigler, and M.F. Elias, pp. 43. New York: Plenum Press (1978).
16. Kahn, R.L., Goldfarb, A.I., Pollack, M. and Peck, A., *Am J Psychiatry* 117, 326-328 (1960).
17. Wechsler, D., *The Measurement of Adult Intelligence*, Third Edition, Baltimore: Williams and Wilkins Company, 1944.
18. Shader, R.I., Harmatz, J.S., Salzman, C., *J Am Geriatr Soc* 22, 107-113 (1974).
19. Jender, D.J., Roch, M. and Booth, R.A., *Anal Biochem* 55, 438-448 (1973).
20. Bock, R.D., *Multivariate Statistical Methods in Behavioral Research*, USA: McGraw-Hill, Inc., 1975.

# Dexpanthenol with Choline Bitartrate in the Treatment of Infantile Colic

Reprinted with permission  
through the Copyright  
Clearance Center

● Fifty infants with colic were treated with Ilopan® Choline-WT. Excellent response was achieved in 72 per cent and there were few side effects.

W. G. BEAUREGARD, MD\*  
West Monroe

THE problem of infantile colic is familiar to any physician who cares for babies. Although only light mention is made of this problem in most pediatric literature, the situation can be very disturbing to both the attending physician and to the parents. A recent discussion<sup>1</sup> on this topic emphasized that much crying which is called colic is actually normal crying which the parents should learn to accept. Many parents commonly mistake the two to six hour daily restless period for colic. This "activity period" or "exercise period" often occurs at the same time each day, usually in the late afternoon or early at night. It is the physician's duty to inform the inexperienced parents of this normal restlessness and to explain that some babies simply cry more than others.<sup>4-5</sup> The laity has unduly labeled many forms of infantile restlessness as "the colic", and each case must be individually evaluated to determine whether or not "true colic" does exist.

## The Colic Syndrome

The syndrome which is usually called "colic" is characterized by prolonged high-pitched screaming associated with alternate forceful flexion and extension of the thighs. The hands are tightly clenched, and on examining these babies one notices a generalized hypertonus of the musculature, or "tension". Breath-holding is not unusual and is often associated with a transient dusky hue of the skin. The eyes are firmly closed, and the forehead is contracted into a frown. The abdomen is

\* Reprint requests to 1607 N. Seventh St., West Monroe, La.

often tight to palpation. There is often a family history of similar hyperirritability during the newborn period of either or both parents. Occasionally, the examiner will detect signs or symptoms of tension in the parents.

## Symptom Complex Subsides in Three Months

The passage of excessive flatus during these episodes is not uncommon; many of these infants are slow to burp or cannot be burped at all. Aerophagia, associated with a marked desire to suck and a voracious appetite, is commonly observed. Sometimes air-swallowing can be heard during feedings. The increased motor activity with a marked sucking reflex may give the impression that the baby interprets his colic pains as hunger pains; this causes more aerophagia with each feeding which results in more colic. Fortunately, this symptom complex usually has subsided by the age of 3 months.<sup>6</sup>

## Aerophagic Colic

The infant under consideration in this study is the one whose colic seems to stem mainly from aerophagia. He may be difficult to burp after feedings, and he may temporarily be unable to pass enough flatus to relieve abdominal distention. Changing nipples, bottles and formulas may offer very little improvement. His rapid intake of formula allows considerable air to be swallowed, regardless of the feeding system used.

## Antispasmodic Drugs Traditional

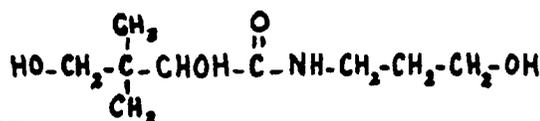
Traditionally, antispasmodic drugs have been the cardinal treatment for colic. In

## TREATMENT OF INFANTILE COLIC—BEAUREGARD

many instances relief or partial relief is afforded by atropine or belladonna derivatives such as dicyclomine hydrochloride, meclizine hydrochloride, hyoscine hydrobromide and others either alone or in combination with barbiturates or other sedatives. Because these agents are often disappointing in relieving colic due to aerophagia, this study was undertaken to evaluate the converse therapeutic approach—that of using an agent which increases intestinal motility rather than one which diminishes it.

### Pharmacology

Dexpanthenol (Dextro-pantothenyl alcohol) is the alcohol analogue of d-pantothenic acid, a member of the B-complex group of vitamins:



(DEXTRO PANTOTHENYL ALCOHOL)

Fig 1.

On the basis of theoretical considerations, dexpanthenol has been used for the prevention and therapy of gastrointestinal atony or distention. The rationale for the use of dexpanthenol is based on the assumption that its administration increases the amount of coenzyme A available for the formation of acetylcholine, which, in turn, increases intestinal tone. So far, no one has conclusively demonstrated that the administration of dexpanthenol will lead to an increase in coenzyme A and acetylcholine; thus, the scientific basis for the use of dexpanthenol has not yet been proved. However, many clinical observers are convinced that it does increase intestinal motility.

Choline is the parent substance of acetylcholine, a neurohumoral substance required for gastrointestinal tonus and peristaltic efficiency.

### Side Effects

No untoward effects have been reported with the use of dexpanthenol even when large doses were administered; thus the agent appears to be relatively nontoxic.

The only known contraindication to the use of dexpanthenol is hemophilia, in which it may have a tendency to prolong bleeding time. Theoretical considerations suggest that dexpanthenol should not be used for at least 12 hours after parasympathomimetic drugs have been administered. Respiratory embarrassment was observed in one case report when dexpanthenol was administered shortly after succinylcholine therapy.

The only side effects observed during this study were an occasional increase in frequency of defecation and in three cases, some mild diarrhea which subsided when the drug was withdrawn (Table 1).

TABLE 1

| Side Effects   | Number of Cases | Percentage |
|----------------|-----------------|------------|
| Mild Diarrhea: | 3               | 6          |

### Method

Fifty infants were individually evaluated at various times during their first 3 months of life. All colic was considered to be related to aerophagia, increased sucking activity, and an unusually voracious appetite with rapid intake of feedings. The parents were questioned closely regarding feeding habits, feeding techniques, variety of foods, family history of colic and the general and specific behavior of the infants before, during and after feedings. Cases in which colic was not thought to be due to aerophagia were excluded from the study group. In all instances the parents affirmed that smacking noises or air swallowing could be heard during feedings. Very often, colic was noted soon after feedings and was associated with increased expulsion of flatus.

Each infant had previously been treated with an antispasmodic-sedative combination in the usual therapeutic amounts with only partial or no improvement in symptoms. The drugs initially used were either methscopolamine bromide, dicyclomine hydrochloride, meclizine hydrochloride, or hyoscine hydrobromide (each combined with phenobarbital). In some cases refractive to these drugs other antispasmodic-sedative combinations were used

unsuccessfully. Usually, this was done when a hyperirritability reaction due to the phenobarbital was suspected.

When symptoms and signs did not disappear with the original therapy, the infants were placed on dexpanthenol with choline bitartrate (Ilopan® Choline-WT) alone. Because this product is presently available only in tablet form, the drug was crushed and mixed in Serpalta or raspberry syrup so that one teaspoonful of syrup was the equivalent of one tablet (50 mgm Ilopan and 25 mgm choline bitartrate). Refrigeration was recommended in order to prevent overgrowth of mold or other contaminants. The dosage for all infants was one teaspoonful (one tablet) every eight hours.

Parents were asked to report on the effectiveness of the drug four to five days after beginning therapy. They were specifically asked to watch for:

- 1) Any improvement of signs and symptoms of colic—especially less crying, less restlessness, less abdominal distention.
- 2) Increased expulsion of flatus.
- 3) Side effects—especially increased frequency or loosening of stools.

#### Comment

This study was undertaken to evaluate the effectiveness of a drug which increases intestinal motility in relieving infantile colic due to retained gas and swallowed air. Admittedly, this report is highly subjective, depending greatly on the opinions of the parents so that "outside factors" must be considered. The parents, for example, might conceivably have been more relaxed because they were using a medication which they felt would solve the problem. This lessening of anxiety could have created a more relaxed environment for the infant and possibly improved his colic. Of some significance, however, is the fact that all infants had been previously treated with at least one of several antispasmodic-sedative combinations with only partial or no relief of colic symptoms.

Most of the infants were treated in the first month of life but an occasional case

was first evaluated during the second month. Since colic is a temporary condition, there is always the possibility that improvement occurred spontaneously.

Fifty colicky infants were treated and observed mainly to determine whether any relief could be obtained after an unsatisfactory response to antispasmodic therapy. This is not to suggest that antispasmodic-sedative combinations are usually inadequate; to the contrary, many cases of colic are afforded much relief by the usual agents. There are some affected infants, however, who seem to obtain relief mainly by expulsion of flatus with increased bowel tone. That 72 per cent of infants in this group showed improvement suggests that carefully controlled studies on a large scale might be worthwhile.

#### Results

Since this was not a "double-blind study", the subjective data obtained from the parents were compiled and arranged in three very general categories: excellent, fair, and poor (Table 2).

TABLE 2

| Categories | Number of Cases | Percentage |
|------------|-----------------|------------|
| Excellent  | 36              | 72         |
| Fair       | 11              | 22         |
| Poor       | 3               | 6          |
| Total:     | 50              | 100        |

An "excellent" response was considered one in which marked improvement in crying, restlessness, abdominal distention, and expulsion of flatus afforded complete or near complete relief of colic with only occasional recurrent episodes noted.

A "fair" response was one in which restlessness and crying showed slight or temporary improvement, although increased frequency and amount of flatus were obvious.

The "poor" category included the cases in which the parents were able to observe no improvement of any type.

Colic is a troublesome syndrome but it cannot be considered as dangerous to the infant. For this reason any therapeutic approach must be reasonably safe with no serious side effects. The excellent safety

## TREATMENT OF INFANTILE COLIC—BEAUREGARD

record of dexpanthenol-choline would lend support to its use in infants with aerophagia and colic. Should further studies confirm its efficacy, another advantage would be the prospect of relatively prolonged therapy with no likelihood of addiction.

### Summary

Fifty infants with colic apparently related to aerophagia and retained intestinal gas were treated with three daily doses of dexpanthenol-choline. All cases had responded poorly to antispasmodic-sedative combinations.

Thirty-six of 50 (72%) infants had an excellent response to treatment with less crying, less restlessness, and more expulsion of flatus.

No serious side effects were noted.

It is hoped that further experience with dexpanthenol-choline in the treatment of

aerophagia and colic in infants may confirm the safety and effectiveness of this drug.

### Acknowledgment

I wish to thank Dr. Paul F. Geiger and Dr. T. H. Eickholt of the Northeast Louisiana State College of Pharmacy for their assistance.

### References

1. Hill, Lee Forrest: Infant Feeding: Historical and Current, *Pediat Clin N Amer* 14:263-265, 1967.
2. Wessel, Morris A.; Cobb, John C.; Jackson, Edith B.; Harris, George S., Jr.; and Detwiler, Ann C.: Paroxysmal Fussing in Infancy, Sometimes Called "Colic", *Pediatrics* 14:421-433, 1954.
3. Holt, Emmett L. Jr.; McIntosh, Rustin; and Barnett, Henry L.: *Pediatrics*, New York: Appleton-Century-Crofts, Inc., pp 260-261, 1962.
4. Rambar, A. C.: Colic in Infants—General Considerations, *Pediatrics* 18:829, 1956.
5. Aldrich, C. A.; Sung, C.; and Knop, C.: The Crying of Newly Born Babies. III. The Early Period at Home, *J Pediat* 27:428, 1945.
6. Schaffer, Alexander J.: *Diseases of the Newborn*, ed 2, Philadelphia and London: W. B. Saunders Co., p 785, 1965.



### Consultant Post

"Dr. Irving M. Blatt of New Orleans has been appointed a national consultant in Otolaryngology to the Surgeon General, United States Air Force. Dr. Blatt is professor and head of the Department of Otorhinolaryngology, Louisiana State University School of Medicine, New Orleans. *Times Picayune* (Mar 7) 1968.

**A. INGREDIENT NAME:**

**DIMERCAPTO-1-PROPANESULFONIC (DMPS)**

**B. Chemical Name:**

DL-2, 3-Dimercapto-1-Propanesulfonic

**C. Common Name:**

DMPS, Unithiol, Dimaval, Mercuval

**D. Chemical grade or description of the strength, quality, and purity of the ingredient:**

|                     | <i>(Limit-Min/Max)</i> | <i>(Results)</i> |
|---------------------|------------------------|------------------|
| Assay: (Iodometric) | 95%                    | 98.2%            |

**E. Information about how the ingredient is supplied:**

Fine, white, crystalline powder, odorless

**F. Information about recognition of the substance in foreign pharmacopeias:**

**G. Bibliography of available safety and efficacy data including peer reviewed medical literature:**

Aposhian, H.V. DMSA and DMPS— water soluble antidotes for heavy metal poisoning. *Annual Review of Pharmacology and Toxicology*, 1983; 23: 193-215.

Aposhian, H. V., Maiorino, R. M., and Gonzalez-Ramirez, D. Mobilization of heavy metals by newer, therapeutically useful chelating agents. *Toxicology*. 1995; 97(1-3): 23-28.

Chisolm, J. J. BAL, EDTA, DMSA, and DMPS in the treatment of lead poisoning in children. *Clinical Toxicology*, 1992; 30(4): 493-504.

Torrs-Alanis, O., Garza-Ocanas, L., and Pineyro-Lopez, A. Evaluation of Urinary Mercury Excretion After Administration of 2,3-Dimercapto-1-propane Sulfonic Acid to Occupationally Exposed Men. *Cinical Toxicology*, 1995; 33(6): 717-720.

Aposhian, H. V., Maiorino, R. M., and Rivera, M. Human Studies with the Chelating Agents, DMPS and DMSA. *Clinical Toxicology*, 1992; 30(4): 505-528.

Clarkson, T. W., magos, L., and Cox, C. Tests of Efficacy of Antidotes for Removl of Methylmercury in Human Poisoning during the Iraq Outbreak. *The Journal of Pharmacology and Experimental Therapeutics*. 1981; 218: 74-83.

Reynolds, J. E. *Martindale - The extra Pharmacopeia* (31<sup>st</sup> ed.). London, UK: the Royal Pharmaceutical Society. 1996. 997.

Chisolm, J. J. and Thomas D. J. Use of 2,3-dimercaptopropane-1-Sulfonate in Treatment of Lead Poisoning in Children. *The Journal of pharmacology and Experimental therapeutics*, 1985; 235(3): 665-669.

Maiorino, R. M., Gonzalez-Ramirez, D., and Zuniga-Charles, M. Sodium 2, 3-Dimercaptopropane-1-Sulfonate Challenge Test for Mercury in Humans. III. Urinary Mercury after Exposure to Mercurous Chloride. *The Journal of Pharmacology and Experimental therapeutics*, 1996; 277(2): 938-944.

Moore, D. F., O'Callaghan, C. A., and Berlyne, G. Acute arsenic poisoning: absence of polyneuropathy after treatment with 2, 3-dimercaptopropanesulphonate (DMPS). *Journal of Neurology, Neurosurgery, and Psychiatry*, 1994; 57: 1133-1135.

Hurlbut, K. M., Maiorino, R. M., and Mayersohn, M. Determination and Metabolism of Dithiol Chelating Agents XVI: Pharmacokinetics of 2,3-Dimercapto-1-Propanesulfonate ater Intravenous Administration to Human Volunteers. *The Journal of Pharmacology and Experimental Therapeutics*. 1994; 268(2): 662-668.

Maiorino, R. M., Xu, Z., and Aposhian, H. V. Determination and Metabolism of Dithiol Chelating Agents. XVII. In Humans, Sodium 2,3-Dimercapto-1-Propanesulfonate is Bound to Plasma Albumin Via Mixed Disulfide Formation and is Found in the Urine as Cyclic Polymeric Disulfides. *The Journal of Pharmacology and Experimental Therapeutics*, 1996; 277(1): 375-384.

Aposhian, H. V., Mershon, M. M., and Brinkley, F. B. Anti-lewisite activity and stability of meso-dimercaptosuccinic acid and 2,3-dimercapto-1-propanesulfonic acid. *Life Sciences*, 1982; 31(19): 2149-2156.

Aposhian, H. V. Biological Chelation: 2,3-dimercapto-propanesulfonic acid and meso-deimercaptosuccinic acid. *Adv Enzyme Regul*, 1982;20: 301-319.

**H. Information about dosage forms used:**

Capsules

**I. Information about strength:**

200-400mg

**J. Information about route of administration:**

Orally

**K. Stability data:**

Melts at about 230-235°

Stable

**L. Formulations:**

**M. Miscellaneous Information:**

# CERTIFICATE OF ANALYSIS

30-2205  
# 56228  
Page 1

Date: 02/02/98

PRODUCT: DL-2,3-DIMERCAPTO-1-PROPANESULFONIC ACID SOD -

---

CATALOG NO: YY110 \*\*  
LOT NO: NA0487  
CUSTOMER NO: PRO055

---

| DESCRIPTION               | LIMIT |      | RESULT          |
|---------------------------|-------|------|-----------------|
|                           | MIN.  | MAX. |                 |
| <u>ASSAY (IODOMETRIC)</u> | 95 %  | -    | <u>98.2 %</u> D |



APPROVED BY: Lilian D. Casabar  
LILIAN D. CASABAR

2/98

QUALITY CONTROL REPORT

A CHEMICAL NAME.: DIMERCAPTO-1-PROPANESULFONIC

MANUFACTURE LOT NO.: NA0487

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP \_\_\_/BP \_\_\_/MERCK \_\_\_/NF \_\_\_/MART. \_\_\_/CO. SPECS. \_\_\_.

1) DESCRIPTION.:

E FINE, WHITE, CRYSTALLINE POWDER; ODORLESS.

2) SOLUBILITY.:

FREELY SOLUBLE IN WATER; SLIGHTLY SOLUBLE IN ALCOHOL AND IN METHANOL.

3) MELTING POINT.:

MELTS AT ABOUT 230-235 DEGREE.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

A) COMPLIES IR SPECTRUM AS PER COMPANY SPECS.

PASSES.: \_\_\_\_\_

FAILS.: \_\_\_\_\_

COMMENTS.: FULL NAME.: DIMERCAPTO-1-PROPANESULFONIC ACID SODIUM SALT 2,3.

ANALYST SIGNATURE.: \_\_\_\_\_

DATE.: \_\_\_\_\_

PREPACK TEST.: \_\_\_\_\_

DATE.: \_\_\_\_\_

INITIAL.: \_\_\_\_\_

RETEST.: \_\_\_\_\_

DATE.: \_\_\_\_\_

INITIAL.: \_\_\_\_\_



Use your web browser's "Back" key to return to previous topic.

## MATERIAL SAFETY DATA SHEET

**DI-2,3-Dimercapto-1-Propanesulfonic Acid, Sodium Salt, Monohydrate 95%  
02225**

### \*\*\*\* SECTION 1 - CHEMICAL PRODUCT AND COMPANY IDENTIFICATION \*\*\*\*

MSDS Name: DI-2,3-Dimercapto-1-Propanesulfonic Acid, Sodium Salt, Monohydrate B

Synonyms:  
DMPS

Company Identification: Acros Organics N.V.  
One Reagent Lane  
Fairlawn, NJ 07410

For information in North America, call: 800-ACROS-01  
For emergencies in the US, call CHEMTREC: 800-424-9300  
For emergencies in the US, call CHEMTREC: 800-424-9300

### \*\*\*\* SECTION 2 - COMPOSITION, INFORMATION ON INGREDIENTS \*\*\*\*

| CAS#      | Chemical Name   | %   | EINECS#   |
|-----------|---|-----|-----------|
| 4076-02-2 | DI-2,3-Dimercapto-1-Propanesulfonic Acid, Sodium Salt Monohydrate | 95% | 223-796-3 |

### \*\*\*\* SECTION 3 - HAZARDS IDENTIFICATION \*\*\*\*

#### EMERGENCY OVERVIEW

Appearance: white.

Caution! Air sensitive. The toxicological properties of this material have not been fully investigated.

Target Organs: None known.

#### Potential Health Effects

##### Eye:

No information regarding eye irritation and other potential effects was found.

##### Skin:

No information regarding skin irritation and other potential effects was found.

##### Ingestion:

The toxicological properties of this substance have not been fully investigated.

##### Inhalation:

The toxicological properties of this substance have not been fully investigated. Inhalation of dust may cause respiratory tract

irritation.  
Chronic:  
Not available.

\*\*\*\* SECTION 4 - FIRST AID MEASURES \*\*\*\*

Eyes:  
Flush eyes with plenty of water for at least 15 minutes, occasionally lifting the upper and lower lids. Get medical aid immediately.  
Skin:  
Get medical aid immediately. Flush skin with plenty of soap and water for at least 15 minutes while removing contaminated clothing and shoes.  
Ingestion:  
If victim is conscious and alert, give 2-4 cupfuls of milk or water. Never give anything by mouth to an unconscious person. Get medical aid immediately.  
Inhalation:  
Get medical aid immediately. Remove from exposure to fresh air immediately. If not breathing, give artificial respiration. If breathing is difficult, give oxygen.  
Notes to Physician:  
Treat symptomatically and supportively.

\*\*\*\* SECTION 5 - FIRE FIGHTING MEASURES \*\*\*\*

General Information:  
As in any fire, wear a self-contained breathing apparatus in pressure-demand, MSHA/NIOSH (approved or equivalent), and full protective gear.  
Extinguishing Media:  
Use agent most appropriate to extinguish fire.  
Autoignition Temperature: Not available.  
Flash Point: Not available.  
NFPA Rating: Not published.  
Explosion Limits, Lower: Not available.  
Upper: Not available.

\*\*\*\* SECTION 6 - ACCIDENTAL RELEASE MEASURES \*\*\*\*

General Information: Use proper personal protective equipment as indicated in Section 8.  
Spills/Leaks:  
Sweep up or absorb material, then place into a suitable clean, dry, closed container for disposal. Avoid generating dusty conditions.

\*\*\*\* SECTION 7 - HANDLING and STORAGE \*\*\*\*

Handling:  
Wash thoroughly after handling. Use only in a well ventilated area. Minimize dust generation and accumulation. Avoid contact with eyes, skin, and clothing. Avoid ingestion and inhalation.  
Storage:  
Store in a cool, dry place. Keep container closed when not in use.

\*\*\*\* SECTION 8 - EXPOSURE CONTROLS, PERSONAL PROTECTION \*\*\*\*

Engineering Controls:  
Use adequate ventilation to keep airborne concentrations low.

Exposure Limits

| Chemical Name       | ACGIH       | NIOSH       | OSHA - Final PELs |
|---------------------|-------------|-------------|-------------------|
| DI-2,3-Dimercapto-1 | none listed | none listed | none listed       |
| -Propanesulfonic Ac |             |             |                   |
| id, Sodium Salt Mon |             |             |                   |
| ohydrate            |             |             |                   |

## OSHA Vacated PELs:

DI-2,3-Dimercapto-1-Propanesulfonic Acid, Sodium Salt Monohydrate:  
No OSHA Vacated PELs are listed for this chemical.

## Personal Protective Equipment

## Eyes:

Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133.

## Skin:

Wear appropriate protective gloves to prevent skin exposure.

## Clothing:

Wear appropriate protective clothing to prevent skin exposure.

## Respirators:

Follow the OSHA respirator regulations found in 29CFR 1910.134. Always use a NIOSH-approved respirator when necessary.

## \*\*\*\* SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES \*\*\*\*

Physical State: Solid  
Appearance: white  
Odor: None reported.  
pH: 5.0 0.5  
Vapor Pressure: Not available.  
Vapor Density: Not available.  
Evaporation Rate: Not available.  
Viscosity: Not available.  
Boiling Point: @ 760.00mm Hg  
Freezing/Melting Point: 229 deg C  
Decomposition Temperature: Not available.  
Solubility: Not available.  
Specific Gravity/Density: Not available.  
Molecular Formula: C3H7O3S3Na.H2O  
Molecular Weight: 228.28

## \*\*\*\* SECTION 10 - STABILITY AND REACTIVITY \*\*\*\*

## Chemical Stability:

Stable under normal temperatures and pressures.

## Conditions to Avoid:

Not available.

## Incompatibilities with Other Materials:

Strong oxidizing agents.

## Hazardous Decomposition Products:

Carbon monoxide, oxides of sulfur, carbon dioxide, sodium oxide.

Hazardous Polymerization: Has not been reported.

## \*\*\*\* SECTION 11 - TOXICOLOGICAL INFORMATION \*\*\*\*

## RTECS#:

CAS# 4076-02-2: T26420000

## LD50/LC50:

Not available.

## Carcinogenicity:

DI-2,3-Dimercapto-1-Propanesulfonic Acid, Sodium Salt Monohydrate -

Not listed by ACGIH, IARC, NIOSH, NTP, or OSHA.

## Epidemiology:

No data available.

## Teratogenicity:

No data available.

## Reproductive Effects:

No data available.

## Neurotoxicity:

No data available.

## Mutagenicity:

No data available.

## Other Studies:

No data available.

\*\*\*\* SECTION 12 - ECOLOGICAL INFORMATION \*\*\*\*

Ecotoxicity:  
 Not available.  
 Environmental Fate:  
 Not available.  
 Physical/Chemical:  
 Not available.  
 Other:  
 Not available.

\*\*\*\* SECTION 13 - DISPOSAL CONSIDERATIONS \*\*\*\*

Dispose of in a manner consistent with federal, state, and local regulations.  
 RCRA D-Series Maximum Concentration of Contaminants: Not listed.  
 RCRA D-Series Chronic Toxicity Reference Levels: Not listed.  
 RCRA F-Series: Not listed.  
 RCRA P-Series: Not listed.  
 RCRA U-Series: Not listed.  
 Not listed as a material banned from land disposal according to RCRA.

\*\*\*\* SECTION 14 - TRANSPORT INFORMATION \*\*\*\*

US DOT  
 No information available  
 IMO  
 Not regulated as a hazardous material.  
 IATA  
 Not regulated as a hazardous material.  
 RID/ADR  
 Not regulated as a hazardous material.  
 Canadian TDG  
 No information available.

\*\*\*\* SECTION 15 - REGULATORY INFORMATION \*\*\*\*

US FEDERAL

TSCA  
 CAS# 4076-02-2 is not listed on the TSCA inventory.  
 It is for research and development use only.  
 Health & Safety Reporting List  
 None of the chemicals are on the Health & Safety Reporting List.  
 Chemical Test Rules  
 None of the chemicals in this product are under a Chemical Test Rule.  
 Section 12b  
 None of the chemicals are listed under TSCA Section 12b.  
 TSCA Significant New Use Rule  
 None of the chemicals in this material have a SNUR under TSCA.

SARA

Section 302 (RQ)  
 None of the chemicals in this material have an RQ.  
 Section 302 (TPQ)  
 None of the chemicals in this product have a TPQ.  
 Section 313  
 No chemicals are reportable under Section 313.

Clean Air Act:

This material does not contain any hazardous air pollutants.  
 This material does not contain any Class 1 Ozone depleters.  
 This material does not contain any Class 2 Ozone depleters.

Clean Water Act:

None of the chemicals in this product are listed as Hazardous Substances under the CWA.  
 None of the chemicals in this product are listed as Priority Pollutants under the CWA.  
 None of the chemicals in this product are listed as Toxic Pollutants under the CWA.

OSHA:

None of the chemicals in this product are considered highly hazardous by OSHA.

STATE

Not present on state lists from CA, PA, MN, MA, FL, or NJ.

California No Significant Risk Level:

None of the chemicals in this product are listed.

European/International Regulations

European Labeling in Accordance with EC Directives

Hazard Symbols: Not available.

Risk Phrases:

Safety Phrases:

S 24/25 Avoid contact with skin and eyes.

WGK (Water Danger/Protection)

CAS# 4076-02-2:

Canada

None of the chemicals in this product are listed on the DSL/NDSL list.

WHMIS: Not available.

CAS# 4076-02-2 is not listed on Canada's Ingredient Disclosure List.

Exposure Limits

\*\*\*\* SECTION 16 - ADDITIONAL INFORMATION \*\*\*\*

MSDS Creation Date: 3/07/1992 Revision #3 Date: 9/11/1997

The information above is believed to be accurate and represents the best information currently available to us. However, we make no warranty of merchantability or any other warranty, express or implied, with respect to such information, and we assume no liability resulting from its use. Users should make their own investigations to determine the suitability of the information for their particular purposes. In no way shall Fisher be liable for any claims, losses, or damages of any third party or for lost profits or any special, indirect, incidental, consequential or exemplary damages, howsoever arising, even if Fisher has been advised of the possibility of such damages.

-----

Back to product information.

relatively non-toxic thiocyanate, and thus the detoxification of cyanide.

dosage regimen in adults is 300 mg of sodium thiosulphate (10 mL of a 3% solution) administered intravenously over 3 minutes followed by 100 mg of sodium thiosulphate (50 mL of a 25% solution) administered intravenously over a period of about 10 minutes. A reduced dosage regimen in children is 0.15 to 0.3 g per kg body-weight of a 3% solution of sodium thiosulphate (approximately 4.5 to 10.0 mg per kg) administered by 1.65 mL per kg of a 25% solution of sodium thiosulphate (412.5 mg per kg). The methemoglobin concentration should not exceed 30 to 40% and if symptoms of cyanide toxicity recur, it has been suggested that the injections of nitrite and thiosulphate may be repeated after 30 minutes at half the doses.

Sodium thiosulphate is used as an isotonic 4% solution in the management of extravasation of mustine. It has also been tried in the management of extravasation of some other antineoplastic agents (although this is a contentious area, see p.516).

Sodium thiosulphate has antifungal properties and is used topically in the treatment of pityriasis versicolor, the usual treatment of this infection is described on p.397. Sodium thiosulphate and magnesium thiosulphate are included in mixed preparations for a variety of disorders.

The acceptable daily intake of sodium thiosulphate as a food additive is 700 µg per kg body-weight.

WHO. Evaluation of certain food additives and contaminants—second report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 631* 1978.

WHO. Evaluation of certain food additives and contaminants—seventh report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 696* 1983.

Report of sodium thiosulphate given by intravenous infusion for the incidence of nephrotoxicity associated with intraperitoneal cisplatin, see under Adverse Effects in this monograph, p.552.

**Bromate poisoning.** Sodium thiosulphate has been administered in the treatment of bromate poisoning<sup>1,2</sup> although its efficacy is unclear.<sup>3</sup> Sodium thiosulphate is thought to reduce bromate to the less toxic bromide ion, but experimental evidence is lacking.<sup>3</sup> However, the high morbidity associated with bromate poisoning may justify the use of this relatively innocuous compound in some clinical circumstances.<sup>4</sup>

1. *et al.* Bromate poisoning from ingestion of professional-grade neutralizer. *Clin Pharm* 1988; 7: 66–70.

2. *et al.* Bromate poisoning. *J Pediatr* 1989; 114: 114–115.

3. NE, Keamey TE. Sodium thiosulfate unproven as an antidote. *Clin Pharm* 1988; 7: 570, 572.

4. CE. Sodium thiosulfate unproven as bromate antidote. *Clin Pharm* 1988; 7: 572.

## Preparations

Names of preparations are listed below; details are given in Part 3.

### Preparations

1. Sodium Thiosulphate Injection;

2. Sodium Thiosulfate Injection.

### Proprietary Preparations

1. *et al.* *Ger.*: S-hydrit†.

**Ingredient preparations.** *Aust.*: Schwefelbad Dr Klopfer; *ITC, Canad.*: Adasept; *Fr.*: Arterase; Désintex; Désintexol; *Desintex-Choline*; *Desintex-Pentazol†*; *Digestal†*; *Ger.*: Rhino-Sulfuryl; Sulfo-Thiorine Pantothénique†; *It.*: Corti Jaikal; Jaikal; Jodcalcium-POS†; Phera-Sulfad-Dr. Klopfer N; *Ital.*: Istaglobina†; Salicilato At-*to*; *Zeta-Bat. S.Afr.*: Tripac-Cyano; *Spain*: Artro Gamma *Amro* Gamma Vit B1†; *Artrochemit*; *Nacient Sulf†*; *Yodo* *Switz.*: Blemphamide; Sébo Lotion; Sulfo-Balmiral†; *USA*: Cyanide Antidote Package; Komed†; Tinver.

## Succimer (1058 k)

(BAN, USAN, INN).

DMSA, meso-2,3-Dimercaptosuccinic acid; (R',S')-2,3-Dimercapto-butanedioic acid.

$C_4H_8O_4S_2 = 182.2$ .

304-55-2.

† denotes a preparation no longer actively marketed

## Adverse Effects and Precautions

Succimer may cause gastro-intestinal disorders, skin rashes, increases in serum transaminase, flu-like symptoms, drowsiness, and dizziness. Succimer should be used with caution in patients with impaired renal function or a history of hepatic disease.

## Pharmacokinetics

Following oral administration succimer is rapidly but incompletely absorbed. It undergoes rapid and extensive metabolism and is excreted mainly in the urine with small amounts excreted in the faeces and via the lungs.

## References

- Dan RC, *et al.* Pharmacokinetics of meso-2,3-dimercaptosuccinic acid in patients with lead poisoning and in healthy adults. *J Pediatr* 1994; 125: 309–16.

## Uses and Administration

Succimer is a chelating agent structurally related to dimercaprol (see p.980). It forms water-soluble chelates with heavy metals and is used in the treatment of acute poisoning with lead, arsenic, or mercury.

Succimer may also be used in the management of cystinuria. Succimer, labelled with a radionuclide, is used in nuclear medicine.

In the treatment of lead poisoning, succimer is given by mouth in a suggested dose of 10 mg per kg body-weight or 350 mg per m<sup>2</sup> body-surface area every 8 hours for 5 days then every 12 hours for an additional 14 days. The course of treatment may be repeated if necessary, usually after an interval of not less than 2 weeks. The management of lead poisoning, including the use of succimer, is discussed under Lead, Treatment of Adverse Effects, p.1720.

## Reviews

- Anonymous. Succimer—an oral drug for lead poisoning. *Med Lett Drugs Ther* 1991; 33: 78.
- Mann KV, Travers JD. Succimer, an oral lead chelator. *Clin Pharm* 1991; 10: 914–22.

**Extracorporeal administration.** Extracorporeal infusion of succimer into the arterial blood line during haemodialysis, a procedure known as extracorporeal regional complexing haemodialysis, produced a substantial clearance of mercury in an anuric patient following intoxication with inorganic mercury.<sup>1</sup> Clearance was approximately ten times greater than that achieved with haemodialysis following intramuscular administration of dimercaprol.

- Kostyniak PJ, *et al.* Extracorporeal regional complexing haemodialysis treatment of acute inorganic mercury intoxication. *Hum Toxicol* 1990; 9: 137–41.

## Preparations

Names of preparations are listed below; details are given in Part 3.

### Proprietary Preparations

USA: Chemet.

## Trientine Dihydrochloride (13377 a)

Trientine Dihydrochloride (BAN, INN).

MK-0681; Trien Hydrochloride; Trientine Hydrochloride (USAN); Triethylenetetramine Dihydrochloride, 2,2'-Ethylene-di-iminobis(ethylamine) dihydrochloride; N,N'-bis(2-Aminoethyl)-1,2-ethanediamine dihydrochloride.

$C_8H_{18}N_4 \cdot 2HCl = 219.2$ .

CAS — 112-24-3 (trientine); 38260-01-4 (trientine dihydrochloride).

Pharmacopoeias. In US.

A white to pale yellow crystalline powder. Freely soluble in water; soluble in methyl alcohol; slightly soluble in alcohol; practically insoluble in chloroform and in ether. A 1% solution in water has a pH of 7.0 to 8.5. Store under an inert gas in airtight containers at 2° to 8°. Protect from light.

## Adverse Effects and Precautions

Trientine dihydrochloride may cause iron deficiency. If iron supplements are given an interval of at least 2 hours between the administration of a dose of trientine and iron has been recommended. Recurrence of symptoms of systemic lupus erythematosus has been reported in a patient who had previously reacted to penicillamine.

## Uses and Administration

Trientine dihydrochloride is a copper chelating agent used in a similar way to penicillamine in the treatment of Wilson's disease. It tends to be used in patients intolerant to penicillamine. For a discussion of the management of Wilson's disease see p.992.

Trientine dihydrochloride is administered by mouth, preferably on an empty stomach. The usual initial dose is 750 mg to 1250 mg daily in 2 to 4 divided doses increasing to a maximum of 2 g daily if required. In children, the usual initial dose is 500 to 750 mg daily increasing to a maximum of 1.5 g daily if required.

## Preparations

Names of preparations are listed below; details are given in Part 3.

### Official Preparations

USP 23: Trientine Hydrochloride Capsules.

### Proprietary Preparations

USA: Syprine.

## Unithiol (1059 a)

DMPS, Unithiol, Sodium 2,3-dimercaptopropanesulphonate.

$C_3H_7NaO_3S_3 = 210.3$ .

CAS — 4076-02-2.

Unithiol is a chelating agent structurally related to dimercaprol (see p.980). It is water soluble and reported to be less toxic than dimercaprol. Unithiol is used in the treatment of poisoning by heavy metals including arsenic, lead, inorganic and organic mercury compounds, and chromium. It may be less effective in cadmium poisoning.

Unithiol is given by mouth in doses of 100 mg three times daily. It has also been administered parenterally.

## Reviews

- Aposhian HV. DMSA and DMPS—water soluble antidotes for heavy metal poisoning. *Ann Rev Pharmacol Toxicol* 1983; 23: 193–215.
- Hruby K, Donner A. 2,3-Dimercapto-1-propanesulphonate in heavy metal poisoning. *Med Toxicol* 1987; 2: 317–23.

**Lead poisoning.** Unithiol has been tried in twelve children with chronic lead poisoning.<sup>1</sup> It reduced lead concentrations in blood but did not affect the concentrations of copper or zinc in plasma. During treatment the urinary excretion of lead, copper, and zinc was increased.

The usual chelating agents used in the management of lead poisoning are discussed on p.1720.

- Chisolm JJ, Thomas DJ. Use of 2,3-dimercaptopropane-1-sulphonate in treatment of lead poisoning in children. *J Pharmacol Exp Ther* 1985; 235: 665–9.

**Mercury poisoning.** Administration of unithiol 100 mg twice daily by mouth for a maximum of 15 days enhanced urinary elimination of mercury in 7 patients with mercury poisoning.<sup>1</sup> The urinary elimination of copper and zinc was also increased in most patients and two developed skin rashes. Unithiol, 50 mg per 10 kg body-weight by intramuscular injection three times a day reducing to 50 mg per 10 kg once a day by the third day of treatment, effectively reduced the half-life of mercury in the blood following poisoning with methylmercury.<sup>2</sup>

- Mant TGK. Clinical studies with dimercaptopropane sulphate in mercury poisoning. *Hum Toxicol* 1985; 4: 346.
- Clarkson TW, *et al.* Tests of efficacy of antidotes for removal of methylmercury in human poisoning during the Iraq outbreak. *J Pharmacol Exp Ther* 1981; 218: 74–83.

**Wilson's disease.** Unithiol 200 mg twice daily<sup>1</sup> was used successfully to maintain cupriuresis in a 13-year-old boy with Wilson's disease after he developed systemic lupus during treatment with penicillamine and with trientine dihydrochloride, which are two of the usual agents used in Wilson's disease (see p.992). Unithiol was started in two similar patients but both withdrew from treatment, one because of fever and a fall in leucocyte count following a test dose and the other because of intense nausea and taste impairment.

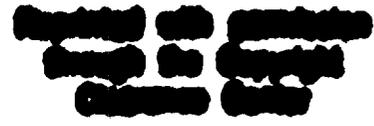
- Walsh JM. Unithiol in Wilson's disease. *Br Med J* 1985; 290: 673–4.

## Preparations

Names of preparations are listed below; details are given in Part 3.

### Proprietary Preparations

*Ger.*: Dimaval, Mercaval.



# 2, 3-DIMERCAPTO-1-PROPANE SULFONIC ACID (DMPS) IN THE TREATMENT OF HEAVY METAL POISONING

*Hong (Rose) Ton Nguyen, Pharm. D. Candidate  
University of Houston  
College of Pharmacy  
Houston, Texas*

February 17 through March 28, 2007

## **2, 3-DIMERCAPTO-1-PROPANE SULFONIC ACID (DMPS) IN THE TREATMENT OF HEAVY METAL POISONING**

### **Introduction**

The use of chelating agents, such as BAL (British Anti-Lewisite), calcium disodium EDTA, and penicillamine in the treatment of human exposure to toxic metals has been well known and accepted (1, 2, 3). However, these chelating agents have limited therapeutic efficacies and undesirable side effects. In the quest for therapeutically more potent and less toxic metal-binding agents to use in the treatment of heavy metal poisoning, scientists have found that the sodium salt of 2, 3-dimercapto-1-propanesulfonic acid (DMPS) is an example of such a compound (2, 4). It is a water-soluble chemical analog of dimercaprol (BAL) but is less toxic. It is administered parenterally and is also effective when given orally. It has been used as an official drug in the Soviet Union since 1958 as Unithiol®. DMPS has been approved by the German Food and Drug Administration (FDA) and is manufactured by Heyl & Co. in Berlin, Germany as Dimaval®. However, it is a relatively new antidote, especially to this country; it is being used in the United States as an investigational drug (2).

### **Chemical Properties**

Structurally, DMPS is related to BAL (Figure 1) (1, 2, 3). It is a sulfonic acid salt with two free sulfhydryl groups (SH-) which form complexes with heavy metals, such as mercury

(Hg), cadmium (Cd), arsenic (As), lead (Pb), copper (Cu), silver (Ag), tin (Sn), and others. It is soluble in water and can be administered parenterally as well as orally. DMPS has a distinct odor; thus, it is recommended to administer the drug in ice cold orange juice or in ice cold apple sauce (3). In addition, stability studies on DMPS are currently not available, but it is considered to be very stable and not readily oxidized during pre-use storage.

### **Therapeutic Use**

As mentioned earlier, DMPS is used in the treatment of poisoning in humans by heavy metals including mercury, arsenic, and lead (Table 1) (2, 6, 8, 9, 10). It is registered with the German FDA for the treatment of mercury poisoning and is in fact sold in Germany without the need of a prescription (2). It has also been used as a mercury challenge or diagnostic test for mercury exposure; it has been found as the ideal agent to detoxify patients that have suffered from mercury toxicity from dental amalgam fillings after the fillings have been removed (1, 5, 6). Moreover, DMPS has been reported to be useful in Wilson's disease in which tissue levels of copper are high. It is given by mouth as a single dose of 300 mg or 100 mg three times daily for as long as 15 days. In the treatment of lead poisoning in children an oral dose of 200 mg to 400 mg of DMPS per meter squared body surface area per day was used effectively without observable adverse drug reactions (8). When given parenterally, 5 mg per kg body weight three times a day was the recommended dose(7).

H  
I  
J

## **Pharmacokinetic Studies**

DMPS has been extensively used in humans both in the Soviet Union and in Germany, and pharmacokinetic data after intravenous (IV) and oral (PO) administration of this drug are widely available (1, 2, 11, 12). Studies have shown that DMPS is distributed both extracellularly and to a smaller extent intracellularly (5, 11). Scientists made an assumption that if the drug appeared in the bile then it must have entered liver cells first, and experiments done in rats proved that DMPS does enter the liver cells in small amounts (5). H  
J

In the plasma, DMPS is found to be about 62.5% bound by protein, mainly albumin, via a disulfide linkage (5, 11, 12). This was elucidated by treating the isolated DMPS-albumin complex from the urine with dithiothreitol (DTT) to give back DMPS, the parent compound. The DMPS-albumin disulfide complex is quite stable and may prolong the heavy metal mobilizing activity of DMPS. As a matter of fact, the half-life of the parent compound was 1.8 hours; whereas, that of altered DMPS was 20 hours.

DMPS is metabolized rapidly and is eliminated in the kidney and bile (4, 5, 11, 12). Hurlbut, *et. al.* (1994) demonstrated that only about 12% or 9%, respectively, of the DMPS concentration detected in the urine is presented as the parent drug after fifteen minutes of IV or PO administration of DMPS, suggesting that the majority of the DMPS in the urine were the metabolites or the oxidized forms of the drug (12). In humans, DMPS is biotransformed or oxidized to acyclic polymeric disulfides (which constitute only 0.5% of the total DMPS disulfides) in the liver and cyclic polymeric disulfides (97% of the total DMPS disulfides) in the bile (Figure 2) (2, 5, 12). The amount of altered or unaltered DMPS was determined

using an assay that employed the chemical known as bromobimane to react with the thiols (Figure 3) (5, 12). Neither bromobimane nor DMPS has a fluorescence, but bromobimane would react with DMPS to form a highly fluorescent bimane derivative. The resulting compound is then analyzed using the technique of HPLC (High-Performance Liquid Chromatography) to detect unaltered molecules. The value of the altered or biotransformed molecules of the drug is then determined by subtracting the value of experimentally determined unaltered forms from the value of experimentally determined total DMPS (5).

Nevertheless, the disulfide group and certainly the sulfonic group are very poor chelators, especially of mercury or lead (12). The two sulfhydryl groups of DMPS are necessary for chelation. DMPS disulfides appear to be transported and reduced to DMPS within the renal tubules in the kidney where chelation of mercury by DMPS increases mercury excretion in the urine.

Oral DMPS appears to be less effective; oral bioavailability of DMPS is about 60% (11). The half-life found for total DMPS in a study after IV administration was approximately 20 hours, which was considerably longer than the half-life of 9.5 hours found for total DMPS after oral administration to humans (11). These values may represent differences in the metabolites produced after oral and IV administration. Other pharmacokinetic parameters of the drug include an elimination half-life of 43 minutes, a volume of distribution (Vd) of 160 ml/kg, and a clearance (CL) of 2.6 ml/min/kg (1, 11).

## **Toxicities**

DMPS is a relatively safe drug and has been used innocuously in Europe for many years (1). In the studies done on DMPS at a dose of 5 mg/kg, some patients developed allergic reactions to the drug. This is usually because the patients have a history of allergies. No anaphylactic shock was seen. Other common side effects experienced by some patients were mild and include nausea, weakness, vertigo, and itching skin. No nephrotoxicity was observed. It also exhibited no mutagenic or teratogenic effects (1). When the dosage was increased to 100 mg/kg, the increased effectiveness was noted, but necrotization and ulcerations often occurred at the site of the subcutaneous (SC) or IV injection. However, when injected IV, DMPS should be given over a five minute period since hypotensive effects are possible when it is given parenterally as a bolus (2).

## **DMPS vs. Other Chelating Agents**

In the treatment of heavy metal poisoning, BAL and calcium disodium EDTA are becoming obsolete. Water-soluble chelating agents like DMSA (succimer, Chemet®) and DMPS are therapeutically more potent and less toxic (1, 2, 5). When compared with D-penicillamine and N-acetyl DL-penicillamine, DMPS was the most effective for clearing mercury from the blood (6). It is more advantageous than DMSA since it has been extensively used in the Soviet Union and in Germany, and capsules for oral use as well as parenteral preparations of DMPS are available. DMSA, on the other hand, is only available

orally, thus, pharmacokinetics of DMSA are somewhat limited. Additionally, DMPS does not cause a redistribution of Hg to the brain like calcium disodium EDTA can. DMPS is more specific than calcium disodium EDTA; at diagnostic doses, DMPS would not be expected to increase the urinary excretion of essential trace elements such as copper and zinc. DMPS is able to enter cells to a certain extent and thus is intermediate in its toxicity. Comparatively, DMSA is the least toxic of the dimercapto chelating agents and has the highest LD<sub>50</sub> since it does not get into cells (Table 2).

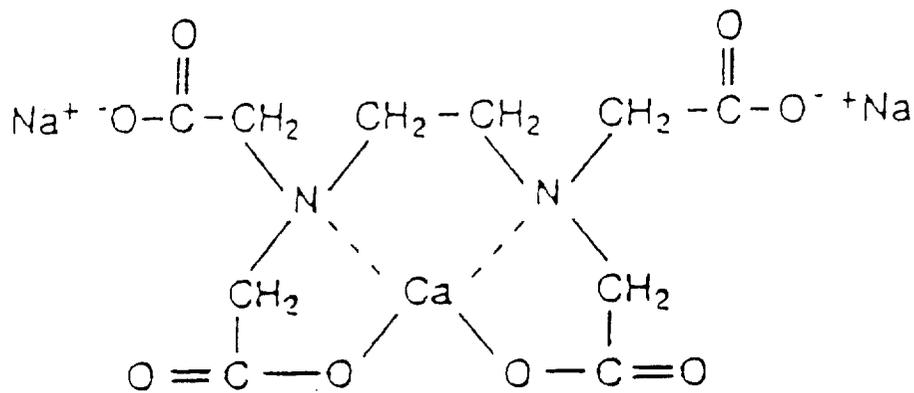
### **Conclusion**

In retrospect, it appears that there is no better chelating agent than DMPS in treating heavy metal poisoning. None of the other chelating agents including DMSA, BAL, penicillamine, or calcium disodium EDTA is as therapeutically diverse and potent in detoxifying patients of heavy metals as DMPS. Other chelating agents are more toxic to use; whereas, DMPS is a relatively safe drug. Thus, in the treatment of heavy metal poisoning 2, 3-dimercapto-1-propane sulfonic acid is the recommended choice.

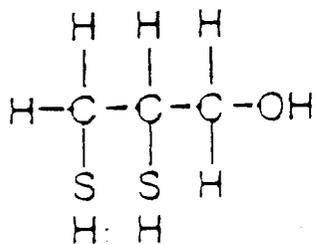
**Figure 1**

Chemical formulas for chelating agents used for treating heavy metal poisoning of humans

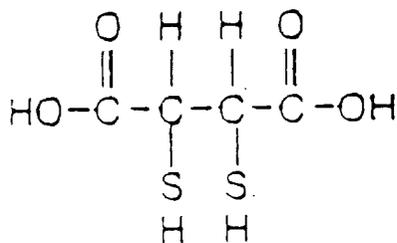
(From Reference #2)



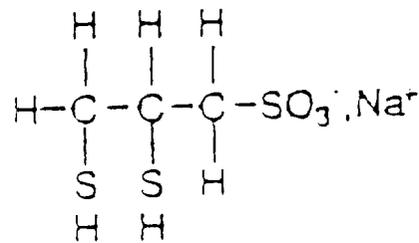
**CaNa<sub>2</sub> EDTA**  
(Edetate Calcium Disodium)



**Dimercaprol**  
(British Antilewisite, BAL)



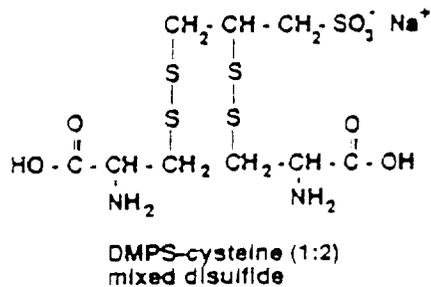
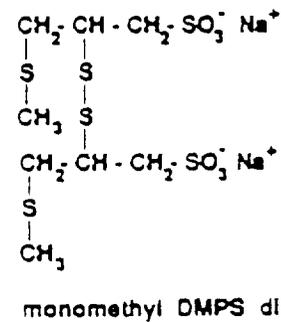
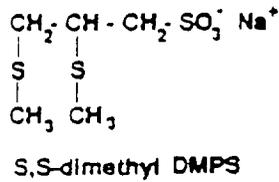
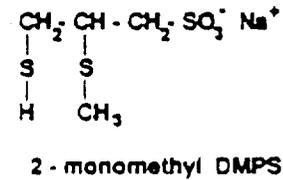
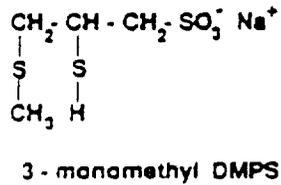
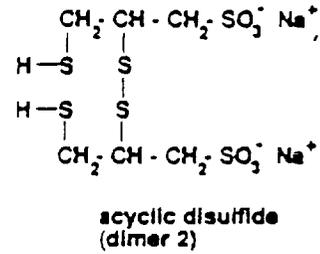
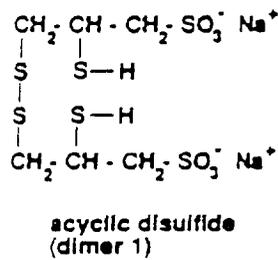
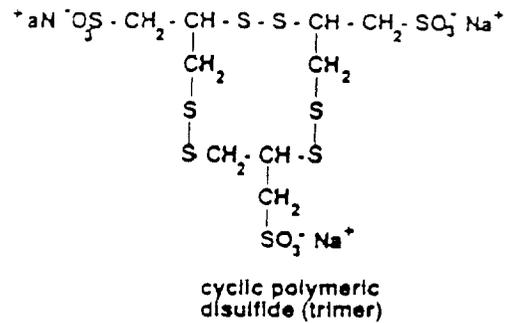
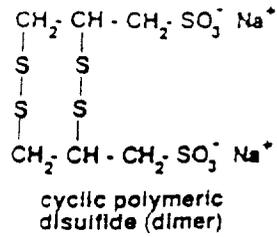
**DMSA**  
(Meso-Dimercapto Succinic Acid)  
Succimer



**DMPS**  
(2,3-Dimercapto-1-Propane-Sulfonic Acid, Na Salt)  
Dimaval

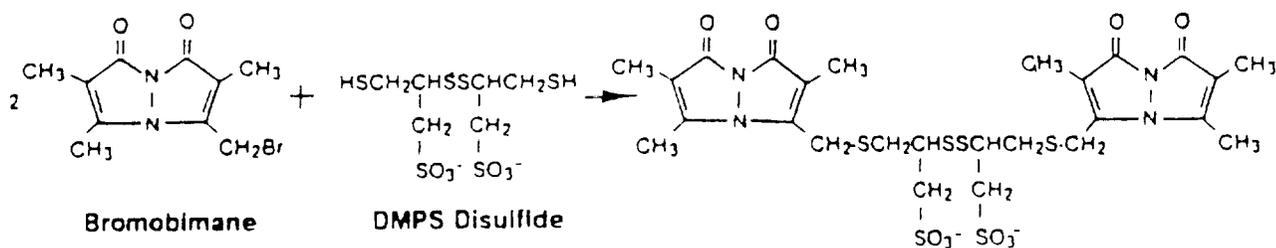
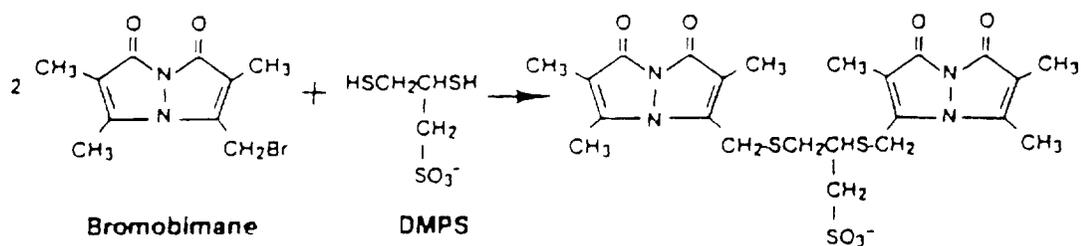
**Figure 2**

Proposed Structures of the human urinary metabolites of DMPS (From Reference # 12)



**Figure 3**

Proposed Reactions of bromobimane with DMPS (From Reference #5)



**Table 1**

Indications and Contraindications of chelating agents in heavy metal poisonings  
(From Reference #2)

| <b>Metal*</b> | <b>First Choice</b> | <b>Second Choice</b> | <b>Contraindications</b> |
|---------------|---------------------|----------------------|--------------------------|
| Hg metal      | DMPS                | DMSA                 | Dimercaprol              |
| Hg inorganic  | DMPS                | DMSA                 | Dimercaprol              |
| Hg organic    | DMSA, DMPS          |                      | Dimercaprol              |
| Pb            | DMSA                | DMPS                 | Dimercaprol, EDTA        |
| As            | DMPS, DMSA          | Dimercaprol          | Dimercaprol (?)          |
| Cr            | DMPS                |                      |                          |
| Sb            | DMPS                |                      |                          |
| Transuranics  | DTPA                |                      |                          |

\*Abbreviations: Hg= mercury, Pb= lead, As= arsenic, Cr=chromium, Sb=antimony.

**Table 2**

\*LD<sub>50</sub> Determination intraperitoneally in mice (From Reference #5)

| Compound  | LD <sub>50</sub> (mmol/kg) | 95% confidence interval | Number of mice |
|-----------|----------------------------|-------------------------|----------------|
| BAL       | 1.48                       | 1.11, 1.97              | 212            |
| DMPA      | 0.82                       | 0.80, 0.84              | 172            |
| DMPS      | 6.53                       | 5.49, 7.71              | 88             |
| meso-DMSA | 13.73                      | 11.36, 15.22            | 164            |

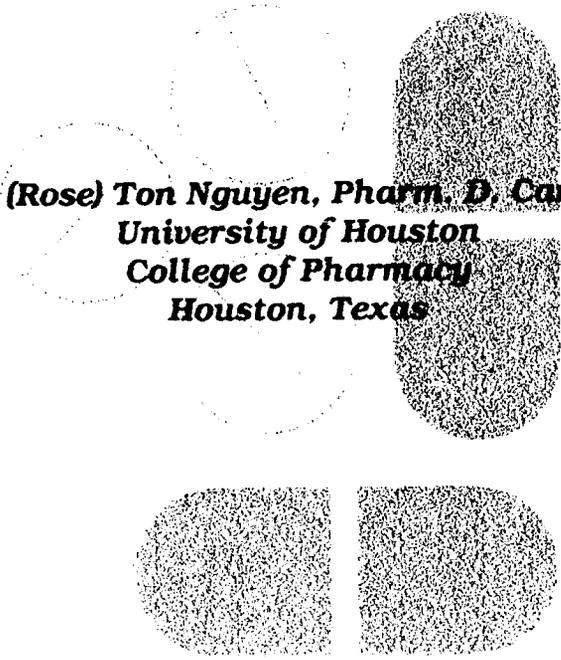
\*LD<sub>50</sub> = median lethal dose.

## REFERENCES

- ✓ - include all references
1. Aposhian, H. V.. DMSA and DMPS -- water soluble antidotes for heavy metal poisoning. *Annual Review of Pharmacology and Toxicology*. (1983). 23: 193-215.
  2. Aposhian, H. V., Maiorino, R. M., Gonzalez-Ramirez, D., et. al.. Mobilization of heavy metals by newer, therapeutically useful chelating agents. *Toxicology*. (1995). 97(1-3): 23-28.
  3. Chisolm, J. J.. BAL, EDTA, DMSA and DMPS in the treatment of lead poisoning in children. *Clinical Toxicology*. (1992). 30(4): 493-504.
  4. Torres-Alanis, O., Garza-Ocanas, L., Pineyro-Lopez, A.. Evaluation of Urinary Mercury Excretion After Administration of 2, 3-Dimercapto-1-propane Sulfonic Acid to Occupationally Exposed Men. *Clinical Toxicology*. (1995). 33(6): 717-720.
  5. Aposhian, H. V., Maiorino, R. M., Rivera, M., et. al.. Human Studies With the Chelating Agents, DMPS and DMSA. *Clinical Toxicology*. (1992). 30(4): 505-528.
  6. Clarkson, T. W., Magos, L., Cox, C., et. al.. Tests of Efficacy of Antidotes for Removal of Methylmercury in Human Poisoning during the Iraq Outbreak. *The Journal of Pharmacology and Experimental Therapeutics*. (1981). 218: 74-83.
  7. Reynolds, J. E. (Ed.). *Martindale - The Extra Pharmacopoeia*. (31st ed.). London, UK: The Royal Pharmaceutical Society. (1996). p. 997.
  8. Chisolm, J. J., Thomas, D. J.. Use of 2, 3-Dimercaptopropane-1-Sulfonate in Treatment of Lead Poisoning in Children. *The Journal of Pharmacology and Experimental Therapeutics*. (1985). 235(3): 665-669.

9. Maiorino, R. M., Gonzalez-Ramirez, D., Zuniga-Charles, M., et. al.. Sodium 2, 3-Dimercaptopropane-1-Sulfonate Challenge Test for Mercury in Humans. III. Urinary Mercury after Exposure to Mercurous Chloride. *The Journal of Pharmacology and Experimental Therapeutics*. (1996). 277(2): 938-944.
10. Moore, D. F., O'Callaghan, C. A., Bertyne, G., et. al.. Acute arsenic poisoning: absence of polyneuropathy after treatment with 2, 3-dimercaptopropanesulphonate (DMPS). *Journal of Neurology, Neurosurgery, and Psychiatry*. (1994). 57: 1133-1135.
11. Hurlbut, K. M., Maiorino, R. M., Mayersohn, M., et. al.. Determination and Metabolism of Dithiol Chelating Agents XVI: Pharmacokinetics of 2, 3-Dimercapto-1-Propanesulfonate after Intravenous Administration to Human Volunteers. *The Journal of Pharmacology and Experimental Therapeutics*. (1994). 268(2): 662-668.
12. Maiorino, R. M., Xu, Z., Aposhian, H. V.. Determination and Metabolism of Dithiol Chelating Agents. XVII. In Humans, Sodium 2, 3-Dimercapto-1-Propanesulfonate is Bound to Plasma Albumin Via Mixed Disulfide Formation and is Found in the Urine as Cyclic Polymeric Disulfides. *The Journal of Pharmacology and Experimental Therapeutics*. (1996). 277(1): 375-384.

**2, 3-DIMERCAPTO-1-PROPANE SULFONIC ACID (DMPS)  
IN THE TREATMENT OF HEAVY METAL POISONING**



**Hong (Rose) Ton Nguyen, Pharm. D. Candidate  
University of Houston  
College of Pharmacy  
Houston, Texas**

February 17 through March 28, 1997

## 2, 3-DIMERCAPTO-I-PROPANE SULFONIC ACID (DMPS) IN THE TREATMENT OF HEAVY METAL POISONING

### Introduction

The use of chelating agents, such as BAL (British Anti-Lewisite), calcium disodium EDTA, and penicillamine in the treatment of human exposure to toxic metals has been well known and accepted (1, 2, 3). However, these chelating agents have limited therapeutic efficacies and undesirable side effects. In the quest for therapeutically more potent and less toxic metal-binding agents to use in the treatment of heavy metal poisoning, scientists have found that the sodium salt of 2, 3-dimercapto-I-propanesulfonic acid (DMPS) is an example of such a compound (2, 4). It is a water-soluble chemical analog of dimercaprol (BAL) but is less toxic. It is administered parenterally and is also effective when given orally. It has been used as an official drug in the Soviet Union since 1958 as Unithiol®. DMPS has been approved by the German Food and Drug Administration (FDA) and is manufactured by Heyl & Co. in Berlin, Germany as Dimaval®. However, it is a relatively new antidote, especially to this country; it is being used in the United States as an investigational drug (2).

### Chemical Properties

Structurally, DMPS is related to BAL (Figure 1) (1, 2, 3). It is a sulfonic acid salt with two free sulfhydryl groups (SH-) which form complexes with heavy metals, such as mercury (Hg), cadmium (Cd), arsenic (As), lead (Pb), copper (Cu), silver (Ag), tin (Sn), and others. It is soluble in water and can be administered parenterally as well as orally. DMPS has a distinct odor; thus, it is recommended to

administer the drug in ice cold orange juice or in ice cold apple sauce (3). In addition, stability studies on DMPS are currently not available, but it is considered to be very stable and not readily oxidized during pre-use storage.

### Therapeutic Use

As mentioned earlier, DMPS is used in the treatment of poisoning in humans by heavy metals including mercury, arsenic, and lead (Table I) (2, 6, 8, 9, 10). It is registered with the German FDA for the treatment of mercury poisoning and is in fact sold in Germany without the need of a prescription (2). It has also been used as a mercury challenge or diagnostic test for mercury exposure; it has been found as the ideal agent to detoxify patients that have suffered from mercury toxicity from dental amalgam fillings after the fillings have been removed (1, 5, 6). Moreover, DMPS has been reported to be useful in Wilson's disease in which tissue levels of copper are high. It is given by mouth as a single dose of 300 mg or 100 mg three times daily for as long as 15 days. In the treatment of lead poisoning in children an oral dose of 200 mg to 400 mg of DMPS per meter squared body surface area per day was used effectively without observable adverse drug reactions (8). When given parenterally, 5 mg per kg body weight three times a day was the recommended dose(7).

### Pharmacokinetic Studies

DMPS has been extensively used in humans both in the Soviet Union and in Germany, and pharmacokinetic data after intravenous (IV) and oral (PO) administration of this drug are widely available (1, 2, 11, 12). Studies have shown that DMPS is distributed both extracellularly and to a smaller extent

intracellularly (5, 11). Scientists made an assumption that if the drug appeared in the bile then it must have entered liver cells first, and experiments done in rats proved that DMPS does enter the liver cells in small amounts (5).

In the plasma, DMPS is found to be about 62.5% bound by protein, mainly albumin, via a disulfide linkage (5, 11, 12). This was elucidated by treating the isolated DMPS-albumin complex from the urine with dithiothreitol (DTT) to give back DMPS, the parent compound. The DMPS-albumin disulfide complex is quite stable and may prolong the heavy metal mobilizing activity of DMPS. As a matter of fact, the half-life of the parent compound was 1.8 hours; whereas, that of altered DMPS was 20 hours.

DMPS is metabolized rapidly and is eliminated in the kidney and bile (4, 5, 11, 12). Hurlbut, *et al.* (1994) demonstrated that only about 12% or 9%, respectively, of the DMPS concentration detected in the urine is presented as the parent drug after fifteen minutes of IV or PO administration of DMPS, suggesting that the majority of the DMPS in the urine were the metabolites or the oxidized forms of the drug (12). In humans, DMPS is biotransformed or oxidized to acyclic polymeric disulfides (which constitute only 0.5% of the total DMPS disulfides) in the liver and cyclic polymeric disulfides (97% of the total DMPS disulfides) in the bile (Figure 2) (2, 5, 12). The amount of altered or unaltered DMPS was determined using an assay that employed the chemical known as bromobimane to react with the thiols (Figure 3) (5, 12). Neither bromobimane nor DMPS has a fluorescence, but bromobimane would react with DMPS to form a highly fluorescent bimane derivative. The resulting compound is then analyzed using the technique of HPLC (High-Performance Liquid Chromatography) to detect unaltered molecules. The value of the altered or biotransformed molecules of the drug is then determined by subtracting the value of experimentally determined unaltered forms from the value of experimentally determined total DMPS (5).

Nevertheless, the disulfide group and certainly the sulfonic group are very poor chelators, especially of mercury or lead (12). The two sulfhydryl groups of DMPS are necessary for chelation. DMPS disulfides appear to be transported and reduced to DMPS within the renal tubules in the kidney where chelation of mercury by DMPS increases mercury excretion in the urine.

Oral DMPS appears to be less effective; oral bioavailability of DMPS is about 60% (11). The half-life found for total DMPS in a study after IV administration was approximately 20 hours, which was considerably longer than the half-life of 9.5 hours found for total DMPS after oral administration to humans (11). These values may represent differences in the metabolites produced after oral and IV administration. Other pharmacokinetic parameters of the drug include an elimination half-life of 43 minutes, a volume of distribution (Vd) of 160 ml/kg, and a clearance (CL) of 2.6 ml/min/kg (1, 11).

### Toxicities

DMPS is a relatively safe drug and has been used innocuously in Europe for many years (1). In the studies done on DMPS at a dose of 5 mg/kg, some patients developed allergic reactions to the drug. This is usually because the patients have a history of allergies. No anaphylactic shock was seen. Other common side effects experienced by some patients were mild and include nausea, weakness, vertigo, and itching skin. No nephrotoxicity was observed. It also exhibited no mutagenic or teratogenic effects (1). When the dosage was increased to 100 mg/kg, the increased effectiveness was noted, but necrotization and ulcerations often occurred at the site of the subcutaneous (SC) or IV injection. However, when injected IV, DMPS should be given over a five minute period since hypotensive effects are possible when it is given

parenterally as a bolus (2).

### DMPS vs. Other Chelating Agents

In the treatment of heavy metal poisoning, BAL and calcium disodium EDTA are becoming obsolete. Water-soluble chelating agents like DMSA (succimer, Chemet®) and DMPS are therapeutically more potent and less toxic (1, 2, 5). When compared with D-penicillamine and N-acetyl DL-penicillamine, DMPS was the most effective for clearing mercury from the blood (6). It is more advantageous than DMSA since it has been extensively used in the Soviet Union and in Germany, and capsules for oral use as well as parenteral preparations of DMPS are available. DMSA, on the other hand, is only available orally, thus, pharmacokinetics of DMSA are somewhat limited. Additionally, DMPS does not cause a redistribution of Hg to the brain like calcium disodium EDTA can. DMPS is more specific than calcium disodium EDTA; at diagnostic doses, DMPS would not be expected to increase the urinary excretion of essential trace elements such as copper and zinc. DMPS is able to enter cells to a certain extent and thus is intermediate in its toxicity.

Comparatively, DMSA is the least toxic of the dimercapto chelating agents and has the highest LD<sub>50</sub> since it does not get into cells (Table 2).

### Conclusion

In retrospect, it appears that there is no better chelating agent than DMPS in treating heavy metal poisoning. None of the other chelating agents including DMSA, BAL, penicillamine, or calcium disodium EDTA is as therapeutically diverse and potent in detoxifying patients of heavy metals as DMPS. Other

chelating agents are more toxic to use; whereas, DMPS is a relatively safe drug. Thus, in the treatment of heavy metal poisoning

2, 3-dimercapto-1-propane sulfonic acid is the recommended choice.

Figure I

Chemical formulas for chelating agents used for treating heavy metal poisoning of humans (From Reference #2)

Figure 2

Proposed Structures of the human urinary metabolites of DMPS (From Reference # 12)

Figure 3

Proposed Reactions of bromobimane with DMPS (From Reference #5)

**Table I**

Indications and Contraindications of chelating agents in heavy metal poisonings  
(From Reference #2)

| Metal*       | First Choice | Second Choice | Contraindications |
|--------------|--------------|---------------|-------------------|
| Hg metal     | DMPS         | DMSA          | Dimercaprol       |
| Hg inorganic | DMPS         | DMSA          | Dimercaprol       |
| Hg organic   | DMSA, DMPS   |               | Dimercaprol       |
| Pb           | DMSA         | DMPS          | Dimercaprol, EDTA |
| As           | DMPS, DMSA   | Dimercaprol   | Dimercaprol (?)   |
| Cr           | DMPS         |               |                   |
| Sb           | DMPS         |               |                   |
| Transuranics | DTPA         |               |                   |

\*Abbreviations: Hg= mercury; Pb= lead; As= arsenic; Cr=chromium; Sb=antimony.

**Table 2**

\*LD<sub>50</sub> Determination intraperitoneally in mice (From Reference #5)

| Compound  | LD <sub>50</sub> (mmol/kg) | 95% confidence interval | Number of mice |
|-----------|----------------------------|-------------------------|----------------|
| BAL       | 1.48                       | 1.11, 1.97              | 212            |
| DMPA      | 0.82                       | 0.80, 0.84              | 172            |
| DMPS      | 6.53                       | 5.49, 7.71              | 88             |
| meso-DMSA | 13.73                      | 11.36, 15.22            | 164            |

\*LD<sub>50</sub> = median lethal dose.

## REFERENCES

1. Aposhian, H. V.. DMSA and DMPS -- water soluble antidotes for heavy metal poisoning. *Annual Review of Pharmacology and Toxicology*. (1983). 23: 193-215.
2. Aposhian, H. V., Maiorino, R. M., Gonzalez-Ramirez, D., et. al.. Mobilization of heavy metals by newer, therapeutically useful chelating agents. *Toxicology*. (1995). 97(1-3): 23-28.
3. Chisolm, J. J.. BAL, EDTA, DMSA and DMPS in the treatment of lead poisoning in children. *Clinical Toxicology*. (1992). 30(4): 493-504.
4. Torres-Alanis, O., Garza-Ocanas, L., Pineyro-Lopez, A.. Evaluation of Urinary Mercury Excretion After Administration of 2, 3-Dimercapto-I-propane Sulfonic Acid to Occupationally Exposed Men. *Clinical Toxicology*. (1995). 33(6): 717-720.
5. Aposhian, H. V., Maiorino, R. M., Rivera, M., et. al.. Human Studies With the Chelating Agents, DMPS and DMSA. *Clinical Toxicology*. (1992). 30(4): 505-528.
6. Clarkson, T. W., Magos, L., Cox, C., et. al.. Tests of Efficacy of Antidotes for Removal of Methylmercury in Human Poisoning during the Iraq Outbreak. *The Journal of Pharmacology and Experimental Therapeutics*. (1981). 218: 74-83.
7. Reynolds, J. E. (Ed.). *Martindale - The Extra Pharmacopoeia*. (3rd ed.). London, UK: The Royal Pharmaceutical Society. (1996). p. 997.
8. Chisolm, J. J., Thomas, D. J.. Use of 2, 3-Dimercaptopropane-I-Sulfonate in Treatment of Lead Poisoning in Children. *The Journal of Pharmacology and Experimental Therapeutics*. (1985). 235(3): 665-669.
9. Maiorino, R. M., Gonzalez-Ramirez, D., Zuniga-Charles, M., et. al.. Sodium 2, 3-

Dimercaptopropane-I-Sulfonate Challenge Test for Mercury in Humans. III. Urinary Mercury after Exposure to Mercurous Chloride. *The Journal of Pharmacology and Experimental Therapeutics*. (1996). 277(2): 938-944.

10. Moore, D. F., O'Callaghan, C. A., Berlyne, G., et. al.. Acute arsenic poisoning: absence of polyneuropathy after treatment with 2, 3-dimercaptopropanesulphonate (DMPS). *Journal of Neurology, Neurosurgery, and Psychiatry*. (1994). 57: 1133- 1135.

11. Hurlbut, K. M., Maiorino, R. M., Mayersohn, M., et. al.. Determination and Metabolism of Dithiol Chelating Agents XVI: Pharmacokinetics of 2, 3-Dimercapto-I-Propanesulfonate after Intravenous Administration to Human Volunteers. *The Journal of Pharmacology and Experimental Therapeutics*. (1994). 268(2): 662- 668.

12. Maiorino, R. M., Xu, Z., Aposhian, H. V.. Determination and Metabolism of Dithiol Chelating Agents. XVII. In Humans, Sodium 2, 3-Dimercapto-I-Propanesulfonate is Bound to Plasma Albumin *Via* Mixed Disulfide Formation and is Found in the Urine as Cyclic Polymeric Disulfides. *The Journal of Pharmacology and Experimental Therapeutics*. (1996). 277(1): 375-384.

Database: Medline <1966 to present>

<1>

Unique Identifier

83087787

Authors

Aposhian HV. Mershon MM. Brinkley FB. Hsu CA. Hackley BE.

Title

Anti-lewisite activity and stability of meso-dimercaptosuccinic acid and 2,3-dimercapto-1-propanesulfonic acid.

Source

Life Sciences. 31(19):2149-56, 1982 Nov 8.

Abstract

Meso-dimercaptosuccinic acid (DMSA) and the sodium salt of 2,3-dimercapto-1-propanesulfonic acid (DMPS) are analogous in chemical structure to dimercaprol (BAL, British Anti-Lewisite). Dimercaprol was among the first therapeutically useful metal chelating agents and was developed originally as an anti-lewisite agent. Either DMSA or DMPS protects rabbits from the lethal systemic action of dichloro(2-chlorovinyl)arsine (29.7  $\mu$ mol/kg, also known as lewisite. The analogs are active in this respect when given either sc or po. The stability of each of the three dimercapto compounds in distilled H<sub>2</sub>O, pH 7.0 at 24 degrees, has been examined for seven days. DMSA retained 82% of its mercapto groups, but no titratable mercapto groups remained in the DMPS or BAL solutions. At pH 5.0, however, there was no striking difference in the stability of the three dimercapto compounds (78-87%) over a seven day period. DMSA and DMPS warrant further investigation as water soluble metal binding agents in both in vivo and in vitro experiments.

K, G  
Please order



**TITLE:** Biological chelation: 2,3-dimercapto-propanesulfonic acid and meso-dimercaptosuccinic acid.

**AUTHOR:** Aposhian HV

**SOURCE:** Adv Enzyme Regul 1982;20:301-19

**NLM CIT. ID:** 82280847

**ABSTRACT:** Water soluble analogs of British Anti-Lewisite that are active orally and less toxic than BAL are now available. These agents are 2,3-dimercapto-1-propanesulfonic acid and meso-dimercaptosuccinic acid. Evidence for their effectiveness in preventing the lethal effects of sodium arsenite in mice and lewisite in rabbits is presented. These analogs can be expected to replace BAL in the treatment of heavy metal poisoning.

9

**MAIN MESH SUBJECTS:** Chelating Agents/\*PHARMACOLOGY  
Dimercaprol/\*ANALOGS & DERIVATIVES/PHARMACOLOGY  
Succimer/\*PHARMACOLOGY  
Sulfhydryl Compounds/\*PHARMACOLOGY  
Unithiol/\*PHARMACOLOGY

**ADDITIONAL MESH SUBJECTS:** Animal  
Arsenic/POISONING  
Cadmium Poisoning  
Lethal Dose 50  
Male  
Mice  
Penicillamine/ANALOGS & DERIVATIVES/PHARMACOLOGY  
Support, Non-U.S. Gov't

**PUBLICATION TYPES:** JOURNAL ARTICLE

**LANGUAGE:** Eng

**REGISTRY NUMBERS:** 0 (Chelating Agents)  
0 (Sulfhydryl Compounds)  
13768-07-5 (sodium arsenite)  
304-55-2 (Succimer)  
4076-02-2 (Unithiol)  
52-67-5 (Penicillamine)  
59-52-9 (Dimercaprol)  
59-53-0 (N-acetylpenicillamine)  
7440-38-2 (Arsenic)

NOTICE  
THIS MATERIAL MAY BE PROTECTED BY  
COPYRIGHT LAW (TITLE 17, U.S. CODE)

BIOLOGICAL CHELATION: 2,3-  
DIMERCAPTO-  
PROPANESULFONIC ACID AND  
MESO-DIMERCAPTOSUCCINIC  
ACID

H. VASKEN APOSHIAN  
Department of Cellular and Developmental Biology,  
University of Arizona, Tucson, AZ 85721

INTRODUCTION

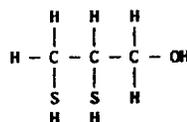
In 1946, summaries of the results of experiments dealing with a new metal binding agent appeared in the biomedical literature. The agent became known as British Anti-Lewisite or BAL. In the U.S. it was given the generic name of dimercaprol. Its importance initially was its effectiveness in treating exposure to the arsenic-containing chemical warfare agent, lewisite. Within a short time, BAL was shown to be useful in the treatment of intoxication by arsenic, lead, mercury and a number of other heavy metals. It was considered to be the long-sought universal antidote for poisoning by one or more of the heavy metals.

In subsequent years due to the increasing clinical experience and to the continuing search for better therapeutic agents, other chelating agents have been introduced (1). Some of these metal-binding agents have replaced one or more of the uses of BAL in clinical medicine. For example D-penicillamine is used to increase the excretion of copper in Wilson's disease (2) and N-acetyl-DL-penicillamine to treat mercury intoxication (3). The exception has been in the treatment of arsenic poisoning. Since the late 1940s, BAL has remained the drug of choice in the U.S. for treating arsenic poisoning (1). BAL, however, is far from the ideal drug. Some of its limitations are listed in Table I.

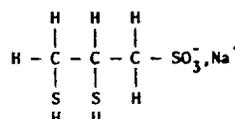
In the mid-1950s, the chelating properties of two new agents, the sodium salt of 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-dimercaptosuccinic acid (DMSA) were reported (4, 5). These compounds are water soluble analogs of BAL whose structures are shown in Figure 1. The synthesis and some of the metal binding properties of DMPS were reported in 1956 by Strunkin (4). DMPS is an official drug of the Soviet Union where it is known as Unithiol. The use of DMSA to increase the uptake of antimony during schistosomiasis therapy was reported by Friedheim *et al*, (5) in 1954. For the

TABLE I. SOME LIMITATIONS OF BRITISH ANTI-LEWISITE

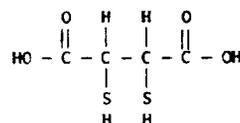
- 
1. High toxicity
  2. Low therapeutic index
  3. Unpleasant side effects
  4. Limited water solubility
  5. Instability in aqueous solution
  6. Must be given by injection
- 

WATER SOLUBLE AND ORALLY ACTIVEANALOGS OF BRITISH ANTILEWISITE

BAL  
(BRITISH ANTILEWISITE)



DMPS  
(2,3-DIMERCAPTO-1-PROPANE-  
SULFONIC ACID, Na SALT)  
UNITHIOL, DIMAVAL



DMSA  
(MESO-DIMERCAPTO SUCCINIC ACID)  
SUCCIMER

FIG. 1. Water soluble and orally active analogs of British Anti-Lewisite.

next 20 years, many reports about the usefulness of these two dimercapto compounds appeared in the biomedical literature of the Soviet Union and mainland China. A few examples of these are cited (6-11). During this time, studies of these compounds by western investigators appear to be virtually nonexistent. (For example, it was not until 1975 that Friedheim and Corvi (12) reported the effectiveness of DMSA in treating mercury poisoning and it was not until 1976 that Gabard (13) reported the use of DMPS in mercury chelation therapy). The reasons for the paucity of earlier studies in the West may be that the synthesis of DMPS is very difficult and its export from the

Soviet to the West was prohibited. In the case of DMSA, although its synthesis is not as difficult, the main reason for a lack of investigative studies in the West appears to be that interest in and funds for chelation research were very limited. DMSA is called Succimer in the Soviet literature.

In about 1978, Heyl & Co., Berlin, succeeded in synthesizing and producing DMPS. This recent availability has encouraged investigators in West Germany, Norway and the U.S. to "rediscover" and study the drug with renewed interest (13-19). DMPS is marketed by Heyl & Co., as Dimaval. It is an approved drug in West Germany for the treatment of mercury intoxication. With the increasing need for safe and convenient chelating agents in clinical medicine, Dimaval should become an important addition to the physician's armamentarium.

The present paper summarizes experiments in this laboratory dealing with the experimental use of DMPS and DMSA in the treatment of poisonings of the following kinds: sodium arsenite in mice, lewisite in rabbits and cadmium

— oride in mice. In addition, a summary of some of the important properties DMPS and DMSA that has been retrieved from the Soviet literature will be discussed.

#### MATERIALS AND METHODS

*Animals.* Male mice of the Swiss CDI strain (randombred Albino) were used in most of the experiments unless otherwise noted. At the time they were used in the experiments, they weighed approximately 25-30 g. Their source of purchase, their food and conditions for maintaining them have been described previously (16, 20).

*Chemicals.* DMPS in the form of its Na salt was a gift of Heyl & Co., Berlin. Since each molecule of NaDMPS has a molecule of H<sub>2</sub>O associated with it, a molecular weight of 228.2 was used in mol calculations. DMSA used for the rabbit studies was pharmaceutical grade and a gift of Johnson and Johnson. The source of the other compounds have been described elsewhere (16, 20).

*Biological studies.* The assay of agents that bind and/or mobilize heavy metals can be based on a number of different measurable responses. The basis of one type of assay is the prevention or reversal of the lethal or toxic effects of the particular heavy metal. A second assay is based on the increased excretion of the metal by the putative metal binding agent. There is, however, increasing evidence that supports still another mechanism. Namely, a metal binding agent sometimes forms an insoluble metabolically-inert complex with the metal. The complex, because of its insolubility, is not excreted from the body. It remains in the cell, metabolically-inert and non-toxic. Therefore, it is possible that some metal binding agent might be life saving without increasing excretion of the metal. This mechanism has been proposed to explain the effectiveness of N-acetyl-DL-penicillamine (21). For these reasons we chose, as

the basis of our initial assays in the present work, the prevention of the lethal action of  $\text{NaAsO}_2$ . Eventually a quantitative comparison will be made of these agents as to their influence on the excretion of  $^{74}\text{As}$ .

The concentrations of the  $\text{NaAsO}_2$  solutions were prepared so that a 25 g animal would receive 0.050 ml. To quantitate the relative effectiveness of a compound in protecting against the lethal effects of  $\text{NaAsO}_2$ , the influence of the administration, i.p., of that compound on the  $\text{LD}_{50}$  of  $\text{NaAsO}_2$  was determined by injecting, s.c., various amounts of  $\text{NaAsO}_2$  dissolved in 0.9% saline. Solutions of the mercapto compounds were prepared immediately before use in 0.9% saline, adjusted to pH 5.5 using NaOH and the concentration adjusted so that a 25 g mouse would receive 0.10 ml. Injections were made using a 0.25 ml glass syringe with a No. 26 needle of 1/2 inch length. For oral administration, curved 18 gauge oral feeding needles, purchased from Popper & Sons, New Hyde Park, N.Y., were used. BAL was dissolved in peanut oil unless otherwise stated.

*Statistical analysis.* When appropriate, experimental results were analyzed using quantal response methodology. A logistic regression model was used to fit the experimental data and parameters were estimated using the BMDP program package (22) on a CDC Cyber 175 digital computer. Median effective dose and corresponding 95% confidence intervals were estimated following Finney (23).

## RESULTS AND DISCUSSION

### *DMPS or DMSA Protects Mice Against the Lethal Effects of Sodium Arsenite*

Mice injected with 0.14 mmols  $\text{NaAsO}_2/\text{kg}$  (an approximate LD 100 dose) and saline, in lieu of mercapto compounds, did not survive (Table 2). The deaths occurred within 48 hr after arsenic administration. DMPS and DMSA are potent antidotes (Table 2) when either agent is given intraperitoneally immediately after  $\text{NaAsO}_2$ . However, two other well-known and clinically useful chelating agents, D-penicillamine and N-acetyl-DL-penicillamine, do not protect (Table 2) under these conditions. The results with these two sulfhydryl compounds are unexpected since there have been two reports of the usefulness of penicillamine in the therapy of arsenic poisoning of humans (24-26).

Neither DMPS nor DMSA need be given immediately after  $\text{NaAsO}_2$ . The administration of either one of the compounds can be delayed at least 2 hr and still be effective (Table 3).

Of greater importance for any therapeutic or prophylactic potential is that DMPS or DMSA is effective even when given orally 15 min prior to the administration of the arsenic compound (Table 4). Under the present experimental conditions, they are effective as oral prophylactics against arsenic intoxication.

TABLE 2. PROTECTION BY DMPS OR DMSA AGAINST THE LETHAL EFFECTS OF SODIUM ARSENITE (16)

| Chelating agent <sup>†</sup><br>(mmoles/kg)<br>i.p. | Cumulative 21-day survival<br>No. surviving/No. started | %    |
|---|---|------|
| (Saline)*   | 0/48  | 0    |
| 0.80 DMPS   | 32/32   | 100  |
| 0.40 DMPS   | 12/12   | 100  |
| 0.25 DMPS   | 24/24   | 100  |
| 0.14 DMPS   | 21/24   | 87.5 |
| 0.07 DMPS   | 19/24   | 79   |
| 0.25 BAL  | 22/24   | 92   |
| 0.14 BAL  | 2/24  | 8    |
| 0.25 DMSA   | 24/24   | 100  |
| 0.14 DMSA   | 20/24   | 83   |
| 0.07 DMSA   | 16/24   | 67   |
| 0.80 D-Pen  | 0/12  | 0    |
| 0.25 D-Pen  | 0/12  | 0    |
| 0.80 N-Ac-DL-Pen                                    | 0/12  | 0    |
| 0.25 N-Ac-DL-Pen                                    | 0/12  | 0    |

\*The NaAsO<sub>2</sub> (0.14 mmoles/kg) was injected s.c. in the right rear leg.

†The chelating agents were administered i.p. immediately after NaAsO<sub>2</sub>.

In this and subsequent Tables, the data represent the combined results of a number of separate experiments. The data were combined to take advantage of the resulting larger number of animals for the calculation of median doses, the statistical evaluation of data and the more economical use of publication space. Thus, the reason for the number of animals in some groups differing from the number in other groups of the same Table is that very often the combined data are the result of from 2 to 4 separate experiments in which different numbers of animals were used in each experiment. Otherwise, the experiments were performed under identical conditions. None of the mercapto compounds listed in Table 2 are toxic at the doses used and under the conditions of the present experiments.

TABLE 3. EXPERIMENTAL THERAPY WITH DMPS OR DMSA CAN BE DELAYED AFTER ARSENIC POISONING (16)

| Dithiol and time<br>after NaAsO <sub>2</sub> *<br>was given | Cumulative 21-day survival<br>No. surviving/No. started | %  |
|---|---|----|
| (Saline)  | 0/20  | 0  |
| 0.25 DMPS   |   |    |
| at 60 min   | 16/19   | 84 |
| at 90 min   | 18/19   | 95 |
| at 120 min  | 17/20   | 85 |
| 0.25 DMSA   |   |    |
| at 60 min   | 15/19   | 79 |
| at 90 min   | 19/20   | 95 |
| at 120 min  | 11/20   | 55 |

\*All animals received NaAsO<sub>2</sub> (0.14 mmoles/kg) s.c. in the right rear leg. DMPS and DMSA were given i.p. At the start of the experiment, when NaAsO<sub>2</sub> was given, there were 10 animals in each group. However, in 3 of the experimental groups, one animal died before DMPS or DMSA was administered. Therefore, those groups are listed with 19 instead of the 20 started.

TABLE 4. PROPHYLACTIC AND ORAL ACTIVITY OF DMPS OR DMSA (16)

| Thiol compound<br>(mmoles/kg)<br>oral | Cumulative 21-day survival |             | %   |
|---------------------------------------|----------------------------|-------------|-----|
|                                       | No. surviving              | No. started |     |
| Saline                                | 0                          | 28          | 0   |
| 1.0 DMPS*                             | 16                         | 18          | 89  |
| 0.75 DMPS                             | 8                          | 10          | 80  |
| 0.50 DMPS                             | 16                         | 20          | 80  |
| 0.25 DMPS                             | 17                         | 20          | 85  |
| 0.12 DMPS                             | 0                          | 10          | 0   |
| 1.0 DMSA                              | 8                          | 8           | 100 |
| 0.50 DMSA                             | 10                         | 10          | 100 |
| 0.25 DMSA                             | 8                          | 10          | 80  |
| 0.12 DMSA                             | 4                          | 10          | 40  |

The  $\text{NaAsO}_2$  (0.14 mmoles/kg) was administered s.c. in the right rear leg. DMPS or DMSA was given orally 15 min prior to the  $\text{NaAsO}_2$ .

\*The survival of control animals receiving 1.0 mmoles of DMPS per kg and saline, instead of  $\text{NaAsO}_2$ , was 100%.

The experiments summarized in Tables 2 to 4 demonstrate the effectiveness of DMPS and DMSA in protecting mice against the lethal action of arsenic. There does not appear to be a great difference between the effectiveness of these two agents under the present conditions. However, it is clear that D-penicillamine and N-acetyl-DL-penicillamine are without beneficial properties against the lethal effects of arsenic under the conditions used in these experiments. Although to our knowledge, arsenic chelate stability constants have not been determined for DMPS or DMSA, such constants, as well as the influence of DMPS in stimulating arsenic excretion, would be valuable in designing and determining the most effective chelating agent for therapy of arsenic poisoning.

Meanwhile, the relative effectiveness of a number of metal binding agents, with particular emphasis on DMPS and DMSA, has been evaluated quantitatively by determining their activity in changing the  $\text{LD}_{50}$  of  $\text{NaAsO}_2$  in mice. In addition, the therapeutic index of DMPS and DMSA has been determined.

#### *DMPS or DMSA increases the $\text{LD}_{50}$ of $\text{NaAsO}_2$*

The  $\text{LD}_{50}$  of subcutaneously administered  $\text{NaAsO}_2$  was found to be 0.132 and 0.127 mmol/kg in 2 separate experiments. When the data of the 2 experiments were combined and used to determine the  $\text{LD}_{50}$ , it was found to be 0.129 mmol/kg (Table 5). The curve is remarkably steep, having a slope of 40.76, if the proportion survival vs dose model is used. The animals that did not survive usually died within 3 days after injection.

TABLE 5. LD<sub>50</sub> OF SODIUM ARSENITE IN THE MOUSE (20)

| NaAsO <sub>2</sub><br>(mmol/kg, s.c.)                    | Exp. 1<br>Dead<br>Started | Exp. 2<br>Dead<br>Started | Summation<br>Dead<br>Started |
|--|---------------------------|---------------------------|------------------------------|
| 0.08   | 0/8                       | —                         | 0/8                          |
| 0.09   | 0/8                       | —                         | 0/8                          |
| 0.10   | 0/8                       | 0/12                      | 0/20                         |
| 0.11   | 0/8                       | —                         | 0/8                          |
| 0.12   | 1/8                       | 2/12                      | 3/20                         |
| 0.13   | 3/8                       | 7/12                      | 10/20                        |
| 0.14   | 7/8                       | 12/12                     | 19/20                        |
| 0.16   | —                         | 12/12                     | 12/12                        |
| LD <sub>50</sub> (mmol/kg)<br>95% Confidence<br>interval | 0.1315<br>(0.122,0.260)   | 0.1274<br>(0.080,0.131)   | 0.1290<br>(0.125,0.139)      |

One way of quantitating the activity of a drug in overcoming the toxicity of agent is to determine how much the LD<sub>50</sub> of the toxic agent is increased by giving more of the potential therapeutic drug. That is, the toxicity of the toxic agent should decrease by giving the therapeutic agent. When 2 i.p. injections of DMPS (0.80 mmols DMPS/kg/injection) are given, one immediately following and the other 90 min after the NaAsO<sub>2</sub>, the LD<sub>50</sub> of NaAsO<sub>2</sub> is increased approximately 4.2-fold to 0.538 mmol/kg (Table 6). Under the same conditions, but using DMSA instead of DMPS, the LD<sub>50</sub> of NaAsO<sub>2</sub> is increased about 4.4-fold to 0.573 mmol/kg (Table 6). The increase with DMSA is only about 5% more than when DMPS is given. Since the LD<sub>50</sub> of NaAsO<sub>2</sub> plus DMPS falls within the confidence interval of the LD<sub>50</sub> of NaAsO<sub>2</sub> plus DMSA, it appears that the effect of DMPS and DMSA on the LD<sub>50</sub> of NaAsO<sub>2</sub> is essentially the same under these experimental conditions.

#### Determination of Therapeutic Index

It was also of interest to determine and compare the therapeutic index of DMPS and DMSA as a measure of their relative potency. The therapeutic index under these conditions was determined by dividing the LD<sub>50</sub> of the dimercapto compound by its ED<sub>50</sub>. The latter value is defined as the amount of dimercapto compound (mmol/kg) protecting 50% of the animals against the lethal effects of 0.15 mmol NaAsO<sub>2</sub>/kg. The latter dose kills 100% of the animals in this laboratory.

The LD<sub>50</sub> of DMPS, when given i.p., was found to be 5.22 mmols/kg (Table 7). This value is comparable to the value of 5.57 mmols/kg obtained by Kostygov (9) and 5.02 mmols/kg, i.p., in rats, as reported recently by Planas-hne *et al.* (27). For DMSA, the LD<sub>50</sub> is 13.58 mmols/kg (Table 8). It compares favorably with 12.1 mmols/kg, i.p., found in mice by Shih-Chun *et al.* (11) in Shanghai and Peking and 14.0 mmols/kg determined by Matsuda

TABLE 6. DIMERCAPTO-I-PROPANE SULFONATE OR MESO-DIMERCAPTOSUCCINIC ACID INCREASES THE LD<sub>50</sub> OF SODIUM ARSENITE\* (20)

| NaAsO <sub>2</sub><br>(mmol/kg. s.c.) | DMPS                    | DMSA                    |
|---------------------------------------|-------------------------|-------------------------|
|                                       | No. Dead<br>No. Started | No. Dead<br>No. Started |
| 0.35                                  | 0/12                    | 2/24                    |
| 0.40                                  | 5/24                    | 8/24                    |
| 0.45                                  | 0/12                    | 8/36                    |
| 0.46                                  | 2/12                    | —                       |
| 0.50                                  | 8/24                    | 5/24                    |
| 0.55                                  | 13/24                   | 11/36                   |
| 0.60                                  | 18/24                   | 15/36                   |
| 0.65                                  | —                       | 10/12                   |
| 0.70                                  | 23/24                   | 33/36                   |
| 0.75                                  | —                       | 12/12                   |
| LD <sub>50</sub> (mmol/kg)            | 0.538                   | 0.573                   |
| 95% Confidence interval               | (0.492, 0.590)          | (0.443, 0.708)          |

\*DMPS or DMSA, 0.80 mmol. kg, was given, i.p. immediately after and 90 min after NaAsO<sub>2</sub>.

TABLE 7. LD<sub>50</sub> OF DIMERCAPTOPROPANESULFONATE IN MICE (20)

| DMPS<br>(mmols/kg. i.p.)    | Dead<br>Started |
|-----------------------------|-----------------|
| 3.3                         | 0/8             |
| 4.0                         | 0/8             |
| 5.0                         | 7/16            |
| 5.5                         | 5/8             |
| 6.0                         | 7/8             |
| 6.6                         | 15/16           |
| 7.0                         | 8/8             |
| 9.9                         | 8/8             |
| LD <sub>50</sub> (mmols/kg) | 5.22            |
| 95% Confidence interval     | (4.35, 5.51)    |

(10) in Japan. An LD<sub>50</sub> in excess of 16.5 mmols/kg has been reported by Friedheim and Corvi (12). It is not clear whether this latter higher value is due to a difference in the mouse strains used or is due to a higher purity of DMSA. When mice were given NaAsO<sub>2</sub> (0.15 mmol/kg) s.c. and 10 min later were treated, i.p., with different amounts of DMPS, the ED<sub>50</sub> was found to be 0.066 mmol/kg (Table 9). The ED<sub>50</sub> under these conditions for DMSA was 0.065 mmol/kg. The therapeutic index for DMPS or DMSA under these conditions

TABLE 8. LD<sub>50</sub> OF MESO-DIMERCAPTOSUCCINIC ACID IN MICE (20)

| DMSA<br>(mmols/kg, i.p.)                                  | Dead<br>Started         |
|---|-------------------------|
| 6.0   | 0/32                    |
| 12.0  | 8/32                    |
| 13.0  | 6/12                    |
| 14.0  | 9/12                    |
| 16.0  | 19/24                   |
| 18.0  | 17/20                   |
| 24.0  | 32/32                   |
| LD <sub>50</sub> (mmols/kg)<br>95% Confidence<br>interval | 13.58<br>(11.36, 15.22) |

TABLE 9. DETERMINATION OF THE ED<sub>50</sub> AND THERAPEUTIC INDEX OF 2,3-DIMERCAPTO-1-PROPANE SULFONIC ACID, NaSALT, AND MESO-DIMERCAPTOSUCCINIC ACID WHEN GIVEN 10 OR 35 MIN AFTER 0.15 mmols NaAsO<sub>2</sub>/kg (20)

| Dimercapto<br>agent        | DMPS<br>+ 10 min                | DMSA<br>+ 10 min  | DMPS<br>+ 35 min  | DMSA<br>+ 35 min  |
|----------------------------|---------------------------------|-------------------|-------------------|-------------------|
| (mmol/kg, i.p.)            | number surviving/number started |                   |                   |                   |
| 0.010                      | —                               | 0/24              | —                 | 0/12              |
| 0.015                      | 0/36                            | —                 | 3/36              | —                 |
| 0.030                      | 1/36                            | 5/24              | 7/36              | 1/30              |
| 0.040                      | —                               | 6/24              | —                 | —                 |
| 0.045                      | 6/24                            | —                 | 8/24              | —                 |
| 0.050                      | —                               | 10/24             | —                 | —                 |
| 0.060                      | 6/24                            | 13/24             | 18/24             | 5/38              |
| 0.0675                     | 15/24                           | —                 | —                 | —                 |
| 0.070                      | —                               | 9/12              | —                 | —                 |
| 0.075                      | 21/24                           | —                 | —                 | —                 |
| 0.080                      | —                               | 18/24             | —                 | 5/12              |
| 0.090                      | 20/24                           | —                 | 15/24             | 3/10              |
| 0.100                      | —                               | —                 | —                 | 16/28             |
| 0.105                      | 31/36                           | —                 | 30/36             | —                 |
| 0.120                      | 35/36                           | —                 | 34/36             | 8/12              |
| 0.125                      | —                               | 21/24             | —                 | 13/17             |
| 0.150                      | —                               | —                 | —                 | 21/30             |
| 0.160                      | —                               | —                 | —                 | 6/8               |
| 0.200                      | —                               | —                 | —                 | 37/46             |
| 0.300                      | —                               | —                 | —                 | 35/38             |
| ED <sub>50</sub> (mmol/kg) | 0.066                           | 0.065             | 0.061             | 0.119             |
| Confidence<br>interval     | (0.059-<br>0.072)               | (0.040-<br>0.086) | (0.048-<br>0.072) | (0.071-<br>0.164) |
| Therapeutic<br>index       | 79                              | 209               | 86                | 115               |

was 79 and 209, respectively. When the DMPS and DMSA was given 35 min after the  $\text{NaAsO}_2$ , the therapeutic index was found to be 86 and 115, respectively. As can be seen under these conditions, DMSA can be considered to be a more effective agent than DMPS in protecting mice against the lethal effects of  $\text{NaAsO}_2$  under these conditions.

Other metal binding agents were also tested for their activity in protecting against the lethal effects of  $\text{NaAsO}_2$ . Neither D-pen nor N-Ac-DL-Pen changes the  $\text{LD}_{50}$  of  $\text{NaAsO}_2$  significantly at the 95% level of significance (Table 10). Other agents (data not shown) that were also found to be ineffective in this respect are the sodium salt of diethyldithiocarbamate,  $\alpha$ -mercaptopropionylglycine, DL-N-acetylhomocysteinethiolactone, and monomercaptosuccinic acid.

TABLE 10. NEITHER D-PENICILLAMINE NOR N-ACETYL-DL-PENICILLAMINE INCREASED THE  $\text{LD}_{50}$  OF SODIUM ARSENITE (20)

| NaAsO <sub>2</sub><br>(mmols/kg, s.c.) | none              | D-Pen*            | N-Ac-DL-Pen*      |
|--|-------------------|-------------------|-------------------|
|  | Dead<br>Started   | Dead<br>Started   | Dead<br>Started   |
| 0.10                                   | 0/12              | 0/8               | 0/8               |
| 0.12                                   | 2/12              | 5/8               | 1/8               |
| 0.13                                   | 7/12              | 7/8               | 5/8               |
| 0.14                                   | 12/12             | 8/8               | 4/8               |
| 0.16                                   | 12/12             | 8/8               | 8/8               |
| 0.20                                   | —                 | 8/8               | 8/8               |
| $\text{LD}_{50}$ (mmol/kg)             | 0.127             | 0.119             | 0.133             |
| 95% Confidence<br>interval             | (0.080-<br>0.131) | (0.078-<br>0.191) | (0.054-<br>0.142) |

\*D-pen or N-Ac-DL-pen (0.80 mmols/kg) was given, i.p., immediately following and at 90 min after the metal binding agent.

#### *DMPS and DMSA Have Anti-Lewisite Activity*

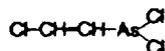
The name British Anti-Lewisite is ingrained very firmly in the mind of most biomedical investigators and physicians. One of the reasons for this is that most medical students and biomedical graduate students are told, in class, at one time or another, of the rational discovery and development of this metal chelating agent as an antidote for lewisite. This almost necessitates that any compound proposed as a replacement of BAL be shown to have anti-lewisite activity. Thus, we have tested DMPS and DMSA for their activity in protecting against the lethal effects of lewisite. The experiments were begun last March in collaboration with Drs. Brennie Hackley, Millard Mershon and Mr. Floyd Brinkley at the BioMed Laboratory at Aberdeen.

Lewisite is an arsenic containing CW agents. It is an oily liquid at 20°. It causes blisters, tissue destruction and blood vessel injury. Systemic poisoning

leading to death is possible. As a CW agent, it is considered to be a moderately delayed casualty agent. Its chemical formula is shown in Figure 2.

Since the introduction of British Anti-Lewisite at the beginning of World War II, all of the therapy of prophylaxis of lewisite has been aimed at chelating the arsenic in the molecule and making it biologically unavailable. This was the basis of Sir Rudolph Peters' search for British Anti-Lewisite.

In the present experiments, the rabbit is anesthetized and then shaved. Using a microliter syringe, lewisite (29.7  $\mu\text{mols/kg}$ ) is injected s.c. The volume of lewisite injected usually amounted to between 7 and 11  $\mu\text{l}$ , depending on the weight of the animal. Table II shows that either DMSA or DMPS will protect rabbits against the lethal effects of lewisite. Using lewisite alone, none of the 6 animals survived. If the animals received 75  $\mu\text{mols DMSA/kg}$  at the times indicated, all of the animals survived. DMSA protects against the lethal systemic effects of lewisite. In the second experiment, only 1 of 6 animals receiving lewisite survived; 66% survived when receiving the 75  $\mu\text{mols DMPS/kg}$  regimen; and 50% of those receiving BAL survived. We do not wish to imply that the effectiveness of these agents against lewisite is in the order of  $\text{DMSA} > \text{DMPS} > \text{BAL}$ . More data are needed before relative effectiveness can be stated.



LEWISITE

(2-CHLOROETHENYL)- ARSONOUS DICHLORIDE

FIG. 2. Chemical formula for lewisite.

TABLE II. DMSA OR DMPS WILL PROTECT RABBITS AGAINST LETHAL EFFECTS OF LEWISITE

| Expt. | $\mu\text{mols/kg}^*$ | 7-day survival<br>survival/start | %   |
|-------|-----------------------|----------------------------------|-----|
| I     | LEW + —               | 0/6                              | 0   |
|       | LEW + 75 DMSA         | 6/6                              | 100 |
| II    | LEW + —               | 1/6                              | 17  |
|       | LEW + 75 DMPS         | 4/6                              | 66  |
|       | LEW + 75 BAL          | 3/6                              | 50  |

\*All agents were given s.c. except BAL, which was given i.m. The stated amount of dimercapto compounds were given at +1', +90', +180', +360' after lewisite and a.m. and p.m. on day 2 and 3.

†29.7  $\mu\text{mols lewisite/kg}$ . These experiments were performed in collaboration with Drs. B. Hackley, M. Mershon and Mr. F. Brinkley.

The data, however, clearly show that DMSA or DMPS will protect rabbits against the lethal effects of lewisite. In this respect the compounds can be said to have Anti-Lewisite activity.

#### *Treatment of Cadmium Toxicity*

Cadmium is virtually ubiquitous. It is deposited and accumulates in most body tissues. It is found in all environmental compartments (air, soil, food and water). The study of cadmium biology has been stimulated by the debilitating osteoporosis of Itai-Itai disease in Japanese adults and the awareness that the increased use of cadmium in industrial and agricultural processes has greatly increased the prevalence of cadmium in the environment (28-30). Along with this, there has been an increased incidence of both acute and chronic cases of clinically identifiable cadmosis (31). In the U.S., although the cadmium content of the human fetus is about 1  $\mu\text{g}$ , the body burden increases approximately 30,000-fold (to about 30 mg) by age 50 years (32).

In experimental acute cadmium poisoning, DTPA or EDTA are marginally effective (30, 33-37) and dimercaptopropanol is contraindicated (37-39). It is astonishing that no accepted dependable effective drugs have become available for treatment of cadmium intoxication, especially since the biological effects of cadmium have been studied intensively during the last 20 years. Thus a number of research groups have been involved recently in a search for an agent to treat cadmium intoxication (18, 30, 41).

I would like to present in a very brief manner some of the unpublished results of my laboratory group as to attempts to find a therapeutically useful cadmium binding agent. DMPS protects mice against the lethal action of cadmium chloride (Tables 12, 13 and 14). Multiple ligand therapy, however, involving  $\text{CdCl}_2$ , DMPS and EDTA is ineffective. These observations (Tables 13 and 14) confirm those of Planas-Bohne (41) and to some extent those of Jones *et al.* (18).

In Table 14 are summarized the results with penicillamine and its analogs. Under the conditions of these experiments neither penicillamine nor any of its analogs so tested were active in protecting against cadmium lethality. Recent work by Yoshida *et al.* (40) with peptide fragments of mouse metallothionein is encouraging and should be extended to test peptide analogs of metallothionein fragments. Our own results are only a beginning and all studies with cadmium lethality and its therapy should be followed by kidney function tests.

#### *Clinical Effectiveness in Man*

Obviously the results of experiments summarized here and elsewhere warrant the continued investigation of these metal binding agents and their

TABLE 12. DMPS PROTECTS MICE AGAINST LETHAL ACTION OF CADMIUM CHLORIDE BUT MULTIPLE LIGAND THERAPY IS INEFFECTIVE

| Group | CdCl <sub>2</sub><br>(mmol/kg)<br>(i.p.) |   | Chelator(s)<br>(mmol/kg)<br>(i.m.)         | Cumulative 28-day survival<br>No. surviving/No. started | %   |
|-------|--|---|--|---|-----|
| I     | 0.06                                     | + | (saline)                                   | 13/56   | 23  |
| II    | 0.06                                     | + | 1.0 DMPS                                   | 19/20   | 95  |
| III   | 0.06                                     | + | 0.4 DMPS                                   | 12/20   | 60  |
| IV    | 0.06                                     | + | 0.2 DMPS                                   | 6/30  | 20  |
| V     | 0.06                                     | + | 0.50 CaNa <sub>2</sub> EDTA                | 12/18   | 67  |
| VI    | 0.06                                     | + | 0.10 CaNa <sub>2</sub> EDTA                | 8/20  | 40  |
| VII   | 0.06                                     | + | 0.05 CaNa <sub>2</sub> EDTA                | 4/18  | 22  |
| VIII  | 0.06                                     | + | 1.0 DMPS &<br>0.50 CaNa <sub>2</sub> EDTA  | 10/10   | 100 |
| IX    | 0.06                                     | + | 0.40 DMPS &<br>0.10 CaNa <sub>2</sub> EDTA | 2/12  | 17  |
| X     | 0.06                                     | + | 0.20 DMPS &<br>0.10 CaNa <sub>2</sub> EDTA | 3/12  | 25  |
| XI    | 0.06                                     | + | 0.20 DMPS &<br>0.05 CaNa <sub>2</sub> EDTA | 3/10  | 30  |
| XII   | (saline)                                 | + | 1.00 DMPS                                  | 9/10  | 90  |

\*The i.m. injections were given 60 min after the i.p. injection of Cd.

†The one animal that did not survive in this group died on Day 21. Death appeared to be the result of fighting.

‡When saline was given i.p. instead of CdCl<sub>2</sub> and any of the following were given i.m. (mmol/kg) the survival was 100%: DMPS (0.80) or (0.20); CaNa<sub>2</sub>EDTA (0.50) or (0.05); DMPS (1.0) & CaNa<sub>2</sub>EDTA (0.5); DMPS (0.20) & CaNa<sub>2</sub>EDTA (0.05).

TABLE 13. DMPS GIVEN ORALLY INCREASES THE SURVIVAL OF MICE RECEIVING CADMIUM CHLORIDE (0.06 mmol/kg) I.P.

| Group   | Time after CdCl <sub>2</sub> that<br>DMPS (1.0 mmol/kg)*<br>was given orally<br>(min) | Cumulative 28-day survival<br>No. surviving/No. started | %   |
|---|---|---|-----|
| I   | -†, -   | 1/16  | 6   |
| II  | +10, +90  | 10/16   | 62  |
| III   | +10, +90  | 13/15   | 87  |
| IV  | - , +90   | 10/16   | 62  |
| The following groups are controls and received saline in place of CdCl <sub>2</sub> |   |   |     |
| V   | +10, -  | 14/16   | 88  |
| VI  | +10, +90  | 16/16   | 100 |
| VII   | - , +90   | 16/16   | 100 |

\*The amount of DMPS given at each time.

†If DMPS was not administered, saline was given in its place.

TABLE 14. NEITHER PENICILLAMINE NOR ITS ANALOGS PROTECT MICE FROM THE LETHAL EFFECTS OF CADMIUM

| Group | CdCl <sub>2</sub><br>(i.p.)<br>(mmol/kg) | Thiol compound<br>(oral)<br>(mmol/kg)* | Min after CdCl <sub>2</sub><br>that thiol cmpd, | Cumulative<br>28-day survival % |
|-------|--|--|---|---------------------------------|
| I     | 0.06                                     | + (saline)                             | —, —, —   | 2/32 6                          |
| II    | 0.06                                     | + 1.0 N-Ac-Pen                         | +10, +90, +180                                  | 1/8 13                          |
| III   | 0.06                                     | + 1.0 N-Ac-Pen                         | +10, + —, + —                                   | 0/8 0                           |
| IV    | (saline)                                 | + 1.0 N-Ac-Pen                         | +10, +90, +180                                  | 8/8 100                         |
| V     | 0.06                                     | + 1.0 D-Pen                            | +10, +90, +180                                  | 15/16 94                        |
| VI    | 0.06                                     | + 1.0 D-Pen                            | +10, + —, + —                                   | 0/8 0                           |
| VII   | 0.06                                     | + 1.0 D-Pen                            | +10, +90, + —                                   | 1/8 12                          |
| VIII  | (saline)                                 | + 1.0 D-Pen                            | +10, + —, + —                                   | 8/8 100                         |
| IX    | (saline)                                 | + 1.0 D-Pen                            | +10, +90, + —                                   | 7/8 88                          |
| X     | (saline)                                 | + 1.0 D-Pen                            | +10, +90, +180                                  | 7/8 88                          |
| XI    | 0.06                                     | + 1.5 N-Ac-thiolisoleuc                | +10, +90, +180                                  | 0/8 0                           |
| XII   | 0.06                                     | + 1.0 N-Ac-thiolisoleuc                | +10, +90, +180                                  | 3/16 19                         |
| XIII  | (saline)                                 | + 1.5 N-Ac-thiolisoleuc                | +10, +90, +180                                  | 6/8 75                          |
| XIV   | 0.06                                     | + 1.0 N-Ac-thiolisoleuc                | +10, + —, + —                                   | 6/8 75                          |
| XV    | (saline)                                 | + 1.0 β-thiolisoleuc                   | +10, + —, + —                                   | 3/8 38                          |
| XVI   | (saline)                                 | + 1.0 β-thiolisoleuc                   | +10, + —, + —                                   | 9/9 100                         |

\*Amount given at each stipulated time.

†These results are the sum of 4 separate experiments.

clinical use in the treatment of heavy metal poisoning. There have been recent reports that confirm their effectiveness in human therapy. DMSA was found to be useful in the treatment of a 46 year-old man who ingested 2000 mg of arsenic in a suicide attempt (42). Treatment with 300 mg DMSA every 6 hr p.o. for 3 days caused an increase in the urinary excretion of arsenic with eventual recovery. DMPS has also been effective in human arsenic poisoning (Wager, personal communication). Friedheim *et al.* (43) in an extension of experiments with experimental animals have reported the effectiveness of DMSA in treating lead poisoning and that it increases the urinary excretion of lead in smelter workers. DMSA was well tolerated and no signs of toxicity were evident. The usefulness of DMPS in the Iraqi mercury disaster has been

TABLE 15. COMPARISON AND SUMMARY OF SOME OF THE INFORMATION ABOUT AND PHARMACOLOGICAL PROPERTIES OF DMPS AND DMSA

| 3-Dimercaptopropane-1-sulfonate, Na salt (DMPS, unithiol, dimaval)   | Meso-2,3-dimercaptosuccinic acid (DMSA, Succimer)  |
|--|--|
| 1. Synthesized in 1950-51 at the Ukrainian Res. Inst. for Health-Chemistry by Petrunkin. Published in 1956 (4).                      | 1. Friedheim, 1954, used Sb-DMSA to increase Sb uptake in schistosomiasis therapy (5). (Intensively studied by mainland Chinese, 1959, for therapy of occupational metal poisoning (11). Primary Soviet investigator since 1965 has been Okomishnikova (50). |
| 2. Crystalline powder, readily soluble in water. Very stable during sterilization and long-term storage.                             | 2. Crystalline powder. Must be brought to pH 5-5.5 before completely soluble in water. Stability during sterilization and long term storage unknown.   |
| 3. Low toxicity, well tolerated even for chronic use, but DMSA is less toxic (20).   | 3. Toxicity is about 2.5 times less than DMPS (20).  |
| 4. Major toxic effect of high dose is hypotension (6, 8).  | 4. Major toxic effect of high dose unknown at present.   |
| 5. Distributed in extracellular space, exclusively (14). Excretion is urinary and rapid (14). Metabolic involvement supposedly none. | 5. Distribution in body compartments unknown at present.   |
| 6. Effective antidote for As, Hg, Sb, Ag, Au, Cu, Cr, Pb, Po, Co, (6, 7, 16, 20, 45-49)  | 6. Effective antidote for As, Pb, Hg, Zn (16, 20, 50-54)   |
| 7. Urinary excretion of Cu and Zn. Increase Fe, Co, Mn or Ni excretion, none or minimal (55).  | 7. Urinary excretion of Co, Fe, Mn, Cu, or Zn. none or minimal (43).   |
| 8. Increase bile flow.   | 8. Effect on bile flow unknown.  |
| 9. Therapeutic dose about 250 mg for 70 kg man.  | 9. Therapeutic dose from 0.5 to 2 g for 70 kg man.   |
| 10. Can be given by mouth, s.c., i.p., i.m., i.v. Only 30-40% of oral dose absorbed from g.i. tract.                                 | 10. Can be given by mouth, s.c., i.p., i.m., i.v. Indications of oral dose being completely absorbed from g.i. tract.  |

documented recently (44). In fact DMPS, as DIMAVAL, is an approved drug in West Germany for the treatment of mercury poisoning.

There are many reports in the Soviet literature dealing with DMPS and DMSA both in experimental conditions or for human therapy. Some of them are cited in the summary of the properties of these two very important metal binding agents listed in Table 15. Obviously, these two water soluble analogs of BAL that are advantageous as to overall effectiveness and low toxicity can be expected to replace virtually all the therapeutic uses of British Anti-Lewisite.

#### SUMMARY

Water soluble analogs of British Anti-Lewisite that are active orally and less toxic than BAL are now available. These agents are 2,3-dimercapto-1-propanesulfonic acid and meso-dimercaptosuccinic acid. Evidence for their effectiveness in preventing the lethal effects of sodium arsenite in mice and lewisite in rabbits is presented. These analogs can be expected to replace BAL in the treatment of heavy metal poisoning.

#### ACKNOWLEDGEMENTS

The author wishes to express his sincere appreciation to Mrs. Linda Boxhorn for her responsible and thoughtful technical assistance and to Heyl and Co. for supplying the DMPS (DIMAVAL). This work was supported by contract DAMD17-80-C-0052 from the USAMRDC. Much of the work reported from the author's laboratory has been published (16, 20).

#### REFERENCES

1. C. D. KLAASEN, Heavy metals and heavy-metal antagonists, pp. 1615-1637 in *The Pharmacological Basis of Therapeutics* (A. G. GILMAN, L. S. GOODMAN and A. GILMAN, eds.), Macmillan, New York (1980).
2. J. M. WALSHE, Penicillamine, a new oral therapy for Wilson's disease, *Am. J. Med.* **21**, 487-495 (1956).
3. H. V. APOSHIAN and M. M. APOSHIAN, N-acetyl-DL-penicillamine, a new oral protective agent against the lethal effects of mercuric chloride, *J. Pharmacol. Exptl. Ther.* **126**, 131-135 (1959).
4. V. E. PETRUNKIN, Synthesis and properties of dimercapto derivatives of alkylsulfonic acids. *Ukr. Khim Zhurn.* **22**, 603-607 (1956).
5. E. FRIEDHEIM, J. R. DASILVA, and A. V. MARTINS, Treatment of Schistosomiasis Mansoni with antimony a-dimercapto-potassium succinate (TWSb), *Am. J. Trop. Med. Hyg.* **3**, 714-727 (1954).
6. S. I. ASHBEL, Unithiol in prophylaxis and therapy of occupation conditioned poisoning with mercury and its organic compounds, pp. 161-168. in *Tiologvye soyedineniya v meditsine* (N. N. LUGANSKIY, V. E. PETRUNKIN, P. V. RODIONOV and A. J. CHERKES, eds.), Kiev: Gos. Med. Izd. Ukrain, SSR. (1959).
7. G. A. BELONOZYKO, Therapeutic action of unithiol in poisoning with inorganic mercury compounds, *Farmakol. i Toksikol.* **21**, 69-73 (1958).

8. L. K. KLIMOVA, Materially k farmakologii unitiola. pp. 135-138 in *Tioloverye soyedineniya v meditsine* (N. N. LUGANSKIY, V. E. PETRUNKIN, P. V. RODIONOV and A. J. CHERKES eds. Gos. Med. Izd. Ukrain. SSR, Kiev (1959).
9. N. M. KOSTYGOV, The antidotal action of mercaptosuccinic acid and Unithiol against mercury, *Farmakol. i. Toksikol.* 21, 64-69 (1958).
10. Y. MATSUDA, Experimental study on sodium dimercaptosuccinic acid, *Gifu Daigaku Igakubu Kiyo* 1, 869-888 (1968).
11. W. SHIH-CHUN, T. KUANG-SHENG and W. CHIH-CHUNG, Chelating therapy with NaDMS in occupational lead and mercury intoxication, *Chin. Med. J.* 84, 437-439 (1965).
12. E. FRIEDHEIM and C. CORVI, Meso-dimercaptosuccinic acid, a chelating agent for the treatment of mercury poisoning, *J. Pharm. Pharmacol.* 27, 624-626 (1965).
13. B. GABARD, Treatment of methylmercury poisoning in the rat with sodium 2,3-dimercaptopropane-1-sulfonate: Influence of dose and mode of administration, *Toxicol. appl. Pharmacol.* 38, 415-424 (1976).
14. B. GABARD, Distribution and excretion of the mercury chelating agent sodium 2,3-dimercaptopropane-1-sulfonate in the rat, *Arch. Toxicol.* 39, 289-298 (1978).
15. G. C. BATTISTONE, R. A. MILLER and M. RUBIN, The use of 2,3-dimercapto-propane sodium sulfonate (DMPS) in mercury chelation therapy. pp. 221-224 in *Clinical Chemistry and Chemical Toxicology of Metals* (S. S. BROWN, ed.) Elsevier Press, (1977).
16. C. H. TADLOCK and H. V. APOSHIAN, Protection of mice against the lethal effects of sodium arsenite by 2,3 dimercapto-1-propane-sulfonic acid and dimercaptosuccinic acid, *Biochem. Biophys. Res. Commun.* 94, 501-507 (1980).
17. W. HAUSER and N. WEGER, Treatment of arsenic poisoning in mice with sodium dimercapto-1-sulfonate, *7th Internatl. Cong. Pharmacol.* Paris, (1978).
18. M. M. JONES, A. D. WEAVER, and W. L. WELLER, The relative effectiveness of some chelating agents as antidotes in acute cadmium poisoning, *Res. Commun. Path. and Pharmacol.* 22, 581-588 (1978).
19. M. M. JONES and M. A. BASINGER, Comparison of standard chelating agents for acute mercuric chloride poisoning in mice, *Res. Commun. Chem. Path. and Pharmacol.* 24, 525-531 (1979).
20. H. V. APOSHIAN, C. H. TADLOCK and T. E. MOON, Protection of mice against the lethal effects of sodium arsenite — A quantitative comparison of a number of chelating agents, *Toxicol. Appl. Pharmacol. (in Press)* (1981).
21. A. CATSCH and A. E. MARMUTH-HOENE, Pharmacology and therapeutic applications of agents used in heavy metal poisoning, pp. 107-224 in *The Chelation of Heavy Metals* (W. G. LEVINE, ed.) Pergamon, Oxford (1979).
22. W. I. DIXON and M. B. BROWN, *Biomedical Computer Program P-Series*, Univ. California Press, Los Angeles (1979).
23. D. J. FINNEY, *Experimental Design and Analysis of Experiments*, The University of Chicago Press, Chicago (1955).
24. R. G. PETERSON and B. H. RUMACH, D-Penicillamine therapy of acute arsenic poisoning, *J. Pediatr.* 91, 661-666 (1977).
25. J. ST. PETERY, O. M. RENNERT, H. CHOI and S. WOLFSON, Arsenic poisoning in childhood, *Clin. Toxicol.* 3, 519-526 (1970).
26. A. KURUVILLA, P. S. BERGESON and A. K. DONE, Arsenic poisoning in childhood — an unusual case report with special notes on therapy with penicillamine, *Clin. Toxicol.* 8, 535-540 (1975).
27. F. PLANAS-BOHNE, B. GABARD and E. H. SCHAFFER, Toxicological studies on sodium 2,3-dimercaptopropane-1-sulfonate in the rat, *Arzheim.-Forsche. Drug Res.* 30, 1291-1294 (1980).
28. *Health Assessment Document for Cadmium*, U.S. Environmental Protection Agency, Washington, D.C., May (1978).
29. *Atmospheric Cadmium: Population Exposure Analysis*, U.S. Environmental Protection Agency, Washington, D.C., March (1978).

30. L. FRIBERG, M. PISCATOR, G. NORDBERG and T. KJELLSTROM, *Cadmium in the Environment*, 2nd Edition, CRC Press, Cleveland, OH (1974).
31. D. F. FLICK, H. F. KHAYBILL and J. M. DIMITROFF, Toxic effects of cadmium: A review. *Environmental Research* 4, 71-85 (1971).
32. M. WEBB and M. DANIEL, Induced synthesis of metallothionein by pig kidney cells *in vitro* in response to cadmium, *Chem. Biol. Interact.* 10, 269-276 (1975).
33. A. CATSCH and A. E. HARMUTH-HOENE, New developments in metal antidotal properties of chelating agents. *Biochem. Pharmacol.* 24, 1557-1562 (1975).
34. D. W. FASSETI, Cadmium: Biological effects and occurrence in the environment. *Ann. Rev. Pharmacol.* 15, 425-435 (1975).
35. L. FRIBERG, M. PISCATOR and C. NORDBERG, *Cadmium in the Environment*, CRC Press, Cleveland, OH (1972).
36. V. EYBL, J. SYKORA and F. MERTL, Effect of CaEDTA and CaDTPA in cadmium intoxication. *Acta biol. med. germ.* 17, 178-185 (1966).
37. B. NIEMEIR, Der einfluss von chelatbildnern auf verteilung und Toxicitat von cadmium. *Int. Arch. Gewerbepath.* 24, 160-168 (1967).
38. J. SCHUBERT, Heavy metals — toxicity and environmental pollution, pp. 239-297 in *Experimental Medicine & Biology*, 40, (S. K. DHAR, ed.), Plenum, New York (1973).
39. R. BERKOW and J. H. TALBOTT, (eds.), *The Merck Manual of Diagnosis and Therapy*, 1974-1981 (Merck Sharp and Dohme Research Laboratories, Rahway, 1977).
40. A. YOSHIDA, B. E. KAPLAN and M. KIMURA, Metal-binding and detoxification effect of synthetic oligopeptides containing three cysteinyl residues, *Proc. Natl. Acad. Sci. U.S.A.* 76, 486-490 (1979).
41. F. PLANAS-BOHNE, Chelate treatment in acute cadmium poisoning. *Experientia* 35, 8-9 (1980).
42. K. LENZ, K. HRUBY, W. DRUML, A. EDER, A. GASZNER, G. KLEINBERGER, M. PICHLER and M. WEISER, 2,3-dimercaptosuccinic acid in human arsenic poisoning. *Arch. Toxicol.* 47, 241-243 (1981).
43. E. FRIEDHEIM, J. H. GRAZIANO, D. POPOVAC, D. DRAGOVIC and B. KUAL, Treatment of lead poisoning by 2,3-dimercaptosuccinic acid. *Lancet* ii, 1234-1235 (1978).
44. T. W. CLARKSON, L. MAGOS, C. COX, M. R. GREENWOOD, L. AMIN-ZAKI, M. A. MAJEED and S. F. AL-DAMLUSI, Test efficacy of antidotes for removal of methylmercury in human poisoning during the Iraq outbreak. *J. Pharmacol. Exptl. Therap.* 248, 74-83 (1981).
45. S. S. ROMANOV, Unithiol as an antidote in pulmonary edema secondary to intravenous injection of silver nitrate. *Farmakol. Toksikol.* 30, 237-238 (1967).
46. E. ANGELOVA and T. STOYTCHIEV, Experimental studies on the antidotal and copper-decorporating effects of Unithiol upon acute poisoning with copper sulfate and the influence of acidoses and alkaloses on these effects. *Bulgarian Acad. Sci.* 15, 179-186 (1973).
47. A. A. SARKISIAN, G. A. EPREMIAN and P. S. SIMAVORIAN, Biochemical and morphologic changes in kidneys in chromium poisoning and therapeutic effectiveness of unithiol. *Zhurnal Eksperimentalnoi i Klinicheskoi Meditsiny.* 11, 25-31 (1971).
48. M. G. ZOTOVA, Effect of unitol on the elimination of  $Po^{210}$ . *Med. Radiologiya* 3, 67-68 (1958).
49. A. I. CHERKES and B. S. BRAVER-CHERNOBULSKAYA, Unithiol — A cobalt antidote. *Farmakol. i Toksikol.* (Moscow), 21, 59-63 (1958).
50. I. Y. OKONISHNIKOVA, Experimental therapy and prophylaxis of acute poisoning with arsenic compounds. *Gig. Tr. Prof. Zabol.* 9, 38-43 (1965).
51. I. Y. OKONISHNIKOVA, E. E. ROZENBERG and I. A. REZINA, The therapeutic-prophylactic effect of succimer in experimental subacute lead acetate poisoning. *Gig. Tr. Prof. Zabol.* 8, 24-28 (1976).
52. J. H. GRAZIANO, D. CUCCIA and E. FRIEDHEIM, The pharmacology of 2,3-dimercaptosuccinic acid and its potential use in arsenic poisoning. *J. Pharmacol. Exptl. Therap.* 207, 1051-1055 (1978).

53. L. MAGOS, The effects of dimercaptosuccinic acid on the excretion and distribution of mercury in rats and mice treated with mercuric chloride and methyl-mercury chloride, *Brit. J. Pharmacol.* **56**, 479-484 (1976).
54. J. AASETH and E. A. H. FRIEDHEIM, Treatment of methyl mercury poisoning in mice with 2,3-dimercaptosuccinic acid and other complexing thiols, *Acta Pharmacol. et Toxicol.* **42**, 248-252 (1978).
55. B. GABARD, F. PLANAS-BOHNE and G. REGULI, The excretion of trace elements in rat urine after treatment with 2,3-dimercaptopropane sodium sulfonate, *Toxicology* **12**, 281-284 (1979).

NOTICE  
THIS MATERIAL MAY BE PROTECTED BY  
COPYRIGHT LAW (TITLE 17, U.S. CODE)

BIOLOGICAL CHELATION: 2,3-  
DIMERCAPTO-  
PROPANESULFONIC ACID AND  
MESO-DIMERCAPTOSUCCINIC  
ACID

H. VASKEN APOSHIAN

Department of Cellular and Developmental Biology,  
University of Arizona, Tucson, AZ 85721

INTRODUCTION

In 1946, summaries of the results of experiments dealing with a new metal binding agent appeared in the biomedical literature. The agent became known as British Anti-Lewisite or BAL. In the U.S. it was given the generic name of dimercaprol. Its importance initially was its effectiveness in treating exposure to the arsenic-containing chemical warfare agent, lewisite. Within a short time, BAL was shown to be useful in the treatment of intoxication by arsenic, lead, mercury and a number of other heavy metals. It was considered to be the long-sought universal antidote for poisoning by one or more of the heavy metals.

In subsequent years due to the increasing clinical experience and to the continuing search for better therapeutic agents, other chelating agents have been introduced (1). Some of these metal-binding agents have replaced one or more of the uses of BAL in clinical medicine. For example D-penicillamine is used to increase the excretion of copper in Wilson's disease (2) and N-acetyl-DL-penicillamine to treat mercury intoxication (3). The exception has been in the treatment of arsenic poisoning. Since the late 1940s, BAL has remained the drug of choice in the U.S. for treating arsenic poisoning (1). BAL, however, is far from the ideal drug. Some of its limitations are listed in Table 1.

In the mid-1950s, the chelating properties of two new agents, the sodium salt of 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-dimercaptosuccinic acid (DMSA) were reported (4, 5). These compounds are water soluble analogs of BAL whose structures are shown in Figure 1. The synthesis and some of the metal binding properties of DMPS were reported in 1956 by Strunkin (4). DMPS is an official drug of the Soviet Union where it is known as Unithiol. The use of DMSA to increase the uptake of antimony during leishmaniasis therapy was reported by Friedheim *et al.*, (5) in 1954. For the

TABLE I. SOME LIMITATIONS OF BRITISH ANTI-LEWISITE

- 
1. High toxicity
  2. Low therapeutic index
  3. Unpleasant side effects
  4. Limited water solubility
  5. Instability in aqueous solution
  6. Must be given by injection
- 

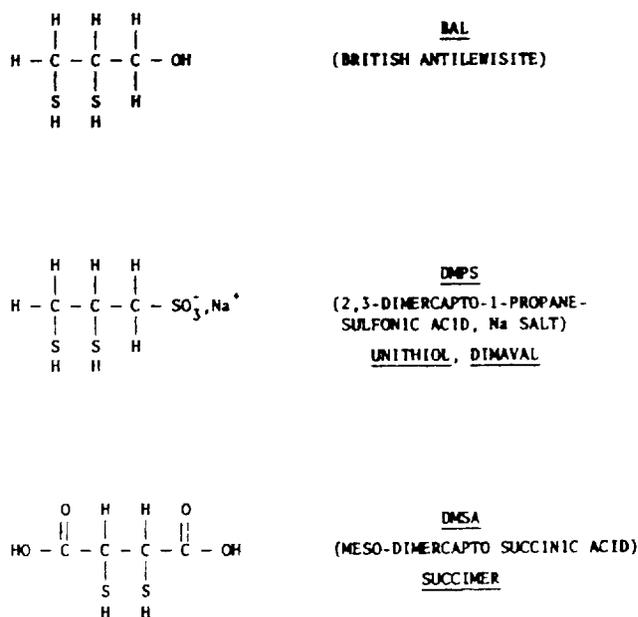
WATER SOLUBLE AND ORALLY ACTIVEANALOGS OF BRITISH ANTI-LEWISITE

FIG. 1. Water soluble and orally active analogs of British Anti-Lewisite.

next 20 years, many reports about the usefulness of these two dimercapto compounds appeared in the biomedical literature of the Soviet Union and mainland China. A few examples of these are cited (6-11). During this time, studies of these compounds by western investigators appear to be virtually nonexistent. (For example, it was not until 1975 that Friedheim and Corvi (12) reported the effectiveness of DMSA in treating mercury poisoning and it was not until 1976 that Gabard (13) reported the use of DMPS in mercury chelation therapy). The reasons for the paucity of earlier studies in the West may be that the synthesis of DMPS is very difficult and its export from the

Soviet to the West was prohibited. In the case of DMSA, although its synthesis is not as difficult, the main reason for a lack of investigative studies in the West appears to be that interest in and funds for chelation research were very limited. DMSA is called Succimer in the Soviet literature.

In about 1978, Heyl & Co., Berlin, succeeded in synthesizing and producing DMPS. This recent availability has encouraged investigators in West Germany, Norway and the U.S. to "rediscover" and study the drug with renewed interest (13-19). DMPS is marketed by Heyl & Co., as Dimaval. It is an approved drug in West Germany for the treatment of mercury intoxication. With the increasing need for safe and convenient chelating agents in clinical medicine, Dimaval should become an important addition to the physician's armamentarium.

The present paper summarizes experiments in this laboratory dealing with the experimental use of DMPS and DMSA in the treatment of poisonings of the following kinds: sodium arsenite in mice, lewisite in rabbits and cadmium chloride in mice. In addition, a summary of some of the important properties of DMPS and DMSA that has been retrieved from the Soviet literature will be discussed.

#### MATERIALS AND METHODS

*Animals.* Male mice of the Swiss CD1 strain (randombred Albino) were used in most of the experiments unless otherwise noted. At the time they were used in the experiments, they weighed approximately 25-30 g. Their source of purchase, their food and conditions for maintaining them have been described previously (16, 20).

*Chemicals.* DMPS in the form of its Na salt was a gift of Heyl & Co., Berlin. Since each molecule of NaDMPS has a molecule of H<sub>2</sub>O associated with it, a molecular weight of 228.2 was used in mol calculations. DMSA used for the rabbit studies was pharmaceutical grade and a gift of Johnson and Johnson. The source of the other compounds have been described elsewhere (16, 20).

*Biological studies.* The assay of agents that bind and/or mobilize heavy metals can be based on a number of different measurable responses. The basis of one type of assay is the prevention or reversal of the lethal or toxic effects of the particular heavy metal. A second assay is based on the increased excretion of the metal by the putative metal binding agent. There is, however, increasing evidence that supports still another mechanism. Namely, a metal binding agent sometimes forms an insoluble metabolically-inert complex with the metal. The complex, because of its insolubility, is not excreted from the body. It remains in the cell, metabolically-inert and non-toxic. Therefore, it is possible that some metal binding agent might be life saving without increasing excretion of the metal. This mechanism has been proposed to explain the effectiveness of N-acetyl-DL-penicillamine (21). For these reasons we chose, as

the basis of our initial assays in the present work, the prevention of the lethal action of  $\text{NaAsO}_2$ . Eventually a quantitative comparison will be made of these agents as to their influence on the excretion of  $^{74}\text{As}$ .

The concentrations of the  $\text{NaAsO}_2$  solutions were prepared so that a 25 g animal would receive 0.050 ml. To quantitate the relative effectiveness of a compound in protecting against the lethal effects of  $\text{NaAsO}_2$ , the influence of the administration, i.p., of that compound on the  $\text{LD}_{50}$  of  $\text{NaAsO}_2$  was determined by injecting, s.c., various amounts of  $\text{NaAsO}_2$  dissolved in 0.9% saline. Solutions of the mercapto compounds were prepared immediately before use in 0.9% saline, adjusted to pH 5.5 using  $\text{NaOH}$  and the concentration adjusted so that a 25 g mouse would receive 0.10 ml. Injections were made using a 0.25 ml glass syringe with a No. 26 needle of 1/2 inch length. For oral administration, curved 18 gauge oral feeding needles, purchased from Popper & Sons, New Hyde Park, N.Y., were used. BAL was dissolved in peanut oil unless otherwise stated.

*Statistical analysis.* When appropriate, experimental results were analyzed using quantal response methodology. A logistic regression model was used to fit the experimental data and parameters were estimated using the BMDP program package (22) on a CDC Cyber 175 digital computer. Median effective dose and corresponding 95% confidence intervals were estimated following Finney (23).

## RESULTS AND DISCUSSION

### *DMPS or DMSA Protects Mice Against the Lethal Effects of Sodium Arsenite*

Mice injected with 0.14 mmols  $\text{NaAsO}_2/\text{kg}$  (an approximate  $\text{LD}_{100}$  dose) and saline, in lieu of mercapto compounds, did not survive (Table 2). The deaths occurred within 48 hr after arsenic administration. DMPS and DMSA are potent antidotes (Table 2) when either agent is given intraperitoneally immediately after  $\text{NaAsO}_2$ . However, two other well-known and clinically useful chelating agents, D-penicillamine and N-acetyl-DL-penicillamine, do not protect (Table 2) under these conditions. The results with these two sulfhydryl compounds are unexpected since there have been two reports of the usefulness of penicillamine in the therapy of arsenic poisoning of humans (24-26).

Neither DMPS nor DMSA need be given immediately after  $\text{NaAsO}_2$ . The administration of either one of the compounds can be delayed at least 2 hr and still be effective (Table 3).

Of greater importance for any therapeutic or prophylactic potential is that DMPS or DMSA is effective even when given orally 15 min prior to the administration of the arsenic compound (Table 4). Under the present experimental conditions, they are effective as oral prophylactics against arsenic intoxication.

TABLE 2. PROTECTION BY DMPS OR DMSA AGAINST THE LETHAL EFFECTS OF SODIUM ARSENITE (16)

| Chelating agent <sup>†</sup><br>(mmoles/kg)<br>i.p. | Cumulative 21-day survival<br>No. surviving/No. started | %    |
|---|---|------|
| (Saline)*   | 0/48  | 0    |
| 0.80 DMPS   | 32/32   | 100  |
| 0.40 DMPS   | 12/12   | 100  |
| 0.25 DMPS   | 24/24   | 100  |
| 0.14 DMPS   | 21/24   | 87.5 |
| 0.07 DMPS   | 19/24   | 79   |
| 0.25 BAL  | 22/24   | 92   |
| 0.14 BAL  | 2/24  | 8    |
| 0.25 DMSA   | 24/24   | 100  |
| 0.14 DMSA   | 20/24   | 83   |
| 0.07 DMSA   | 16/24   | 67   |
| 0.80 D-Pen  | 0/12  | 0    |
| 0.25 D-Pen  | 0/12  | 0    |
| 0.80 N-Ac-DL-Pen                                    | 0/12  | 0    |
| 0.25 N-Ac-DL-Pen                                    | 0/12  | 0    |

\*The NaAsO<sub>2</sub> (0.14 mmoles/kg) was injected s.c. in the right rear leg.

†The chelating agents were administered i.p. immediately after NaAsO<sub>2</sub>.

In this and subsequent Tables, the data represent the combined results of a number of separate experiments. The data were combined to take advantage of the resulting larger number of animals for the calculation of median doses, the statistical evaluation of data and the more economical use of publication space. Thus, the reason for the number of animals in some groups differing from the number in other groups of the same Table is that very often the combined data are the result of from 2 to 4 separate experiments in which different numbers of animals were used in each experiment. Otherwise, the experiments were performed under identical conditions. None of the mercapto compounds listed in Table 2 are toxic at the doses used and under the conditions of the present experiments.

TABLE 3. EXPERIMENTAL THERAPY WITH DMPS OR DMSA CAN BE DELAYED AFTER ARSENIC POISONING (16)

| Dithiol and time<br>after NaAsO <sub>2</sub> *<br>was given | Cumulative 21-day survival<br>No. surviving/No. started | %  |
|---|---|----|
| (Saline)  | 0/20  | 0  |
| 0.25 DMPS   |   |    |
| at 60 min   | 16/19   | 84 |
| at 90 min   | 18/19   | 95 |
| at 120 min  | 17/20   | 85 |
| 0.25 DMSA   |   |    |
| at 60 min   | 15/19   | 79 |
| at 90 min   | 19/20   | 95 |
| at 120 min  | 11/20   | 55 |

\*All animals received NaAsO<sub>2</sub> (0.14 mmoles/kg) s.c. in the right rear leg. DMPS and DMSA were given i.p. At the start of the experiment, when NaAsO<sub>2</sub> was given, there were 10 animals in each group. However, in 3 of the experimental groups, one animal died before DMPS or DMSA was administered. Therefore, those groups are listed with 19 instead of the 20 started.

TABLE 4. PROPHYLACTIC AND ORAL ACTIVITY OF DMPS OR DMSA (16)

| Thiol compound<br>(mmoles/kg)<br>oral | Cumulative 21-day survival |             | %   |
|---------------------------------------|----------------------------|-------------|-----|
|                                       | No. surviving              | No. started |     |
| Saline                                | 0                          | 28          | 0   |
| 1.0 DMPS*                             | 16                         | 18          | 89  |
| 0.75 DMPS                             | 8                          | 10          | 80  |
| 0.50 DMPS                             | 16                         | 20          | 80  |
| 0.25 DMPS                             | 17                         | 20          | 85  |
| 0.12 DMPS                             | 0                          | 10          | 0   |
| 1.0 DMSA                              | 8                          | 8           | 100 |
| 0.50 DMSA                             | 10                         | 10          | 100 |
| 0.25 DMSA                             | 8                          | 10          | 80  |
| 0.12 DMSA                             | 4                          | 10          | 40  |

The  $\text{NaAsO}_2$  (0.14 mmoles/kg) was administered s.c. in the right rear leg. DMPS or DMSA was given orally 15 min prior to the  $\text{NaAsO}_2$ .

\*The survival of control animals receiving 1.0 mmoles of DMPS per kg and saline, instead of  $\text{NaAsO}_2$ , was 100%.

The experiments summarized in Tables 2 to 4 demonstrate the effectiveness of DMPS and DMSA in protecting mice against the lethal action of arsenic. There does not appear to be a great difference between the effectiveness of these two agents under the present conditions. However, it is clear that D-penicillamine and N-acetyl-DL-penicillamine are without beneficial properties against the lethal effects of arsenic under the conditions used in these experiments. Although to our knowledge, arsenic chelate stability constants have not been determined for DMPS or DMSA, such constants, as well as the influence of DMPS in stimulating arsenic excretion, would be valuable in designing and determining the most effective chelating agent for therapy of arsenic poisoning.

Meanwhile, the relative effectiveness of a number of metal binding agents, with particular emphasis on DMPS and DMSA, has been evaluated quantitatively by determining their activity in changing the  $\text{LD}_{50}$  of  $\text{NaAsO}_2$  in mice. In addition, the therapeutic index of DMPS and DMSA has been determined.

#### *DMPS or DMSA increases the $\text{LD}_{50}$ of $\text{NaAsO}_2$*

The  $\text{LD}_{50}$  of subcutaneously administered  $\text{NaAsO}_2$  was found to be 0.132 and 0.127 mmol/kg in 2 separate experiments. When the data of the 2 experiments were combined and used to determine the  $\text{LD}_{50}$ , it was found to be 0.129 mmol/kg (Table 5). The curve is remarkably steep, having a slope of 40.76, if the proportion survival vs dose model is used. The animals that did not survive usually died within 3 days after injection.

TABLE 5. LD<sub>50</sub> OF SODIUM ARSENITE IN THE MOUSE (20)

| NaAsO <sub>2</sub><br>(mmol/kg, s.c.) | Exp. 1<br><u>Dead</u><br>Started | Exp. 2<br><u>Dead</u><br>Started | Summation<br><u>Dead</u><br>Started |
|---------------------------------------|----------------------------------|----------------------------------|-------------------------------------|
| 0.08                                  | 0/8                              | —                                | 0/8                                 |
| 0.09                                  | 0/8                              | —                                | 0/8                                 |
| 0.10                                  | 0/8                              | 0/12                             | 0/20                                |
| 0.11                                  | 0/8                              | —                                | 0/8                                 |
| 0.12                                  | 1/8                              | 2/12                             | 3/20                                |
| 0.13                                  | 3/8                              | 7/12                             | 10/20                               |
| 0.14                                  | 7/8                              | 12/12                            | 19/10                               |
| 0.16                                  | —                                | 12/12                            | 12/12                               |
| LD <sub>50</sub> (mmol/kg)            | 0.1315                           | 0.1274                           | 0.1290                              |
| 95% Confidence<br>interval            | (0.122, 0.260)                   | (0.080, 0.131)                   | (0.125, 0.139)                      |

One way of quantitating the activity of a drug in overcoming the toxicity of an agent is to determine how much the LD<sub>50</sub> of the toxic agent is increased by giving more of the potential therapeutic drug. That is, the toxicity of the toxic agent should decrease by giving the therapeutic agent. When 2 i.p. injections of DMPS (0.80 mmols DMPS/kg/injection) are given, one immediately following and the other 90 min after the NaAsO<sub>2</sub>, the LD<sub>50</sub> of NaAsO<sub>2</sub> is increased approximately 4.2-fold to 0.538 mmol/kg (Table 6). Under the same conditions, but using DMSA instead of DMPS, the LD<sub>50</sub> of NaAsO<sub>2</sub> is increased about 4.4-fold to 0.573 mmol/kg (Table 6). The increase with DMSA is only about 5% more than when DMPS is given. Since the LD<sub>50</sub> of NaAsO<sub>2</sub> plus DMPS falls within the confidence interval of the LD<sub>50</sub> of NaAsO<sub>2</sub> plus DMSA, it appears that the effect of DMPS and DMSA on the LD<sub>50</sub> of NaAsO<sub>2</sub> is essentially the same under these experimental conditions.

#### Determination of Therapeutic Index

It was also of interest to determine and compare the therapeutic index of DMPS and DMSA as a measure of their relative potency. The therapeutic index under these conditions was determined by dividing the LD<sub>50</sub> of the dimercapto compound by its ED<sub>50</sub>. The latter value is defined as the amount of dimercapto compound (mmol/kg) protecting 50% of the animals against the lethal effects of 0.15 mmol NaAsO<sub>2</sub>/kg. The latter dose kills 100% of the animals in this laboratory.

The LD<sub>50</sub> of DMPS, when given i.p., was found to be 5.22 mmols/kg (Table 7). This value is comparable to the value of 5.57 mmols/kg obtained by Kostygov (9) and 5.02 mmols/kg, i.p., in rats, as reported recently by Planas-hne *et al.* (27). For DMSA, the LD<sub>50</sub> is 13.58 mmols/kg (Table 8). It compares favorably with 12.1 mmols/kg, i.p., found in mice by Shih-Chun *et al.* (11) in Shanghai and Peking and 14.0 mmols/kg determined by Matsuda

TABLE 6. DIMERCAPTO-I-PROPANE SULFONATE OR MESO-DIMERCAPTOSUCCINIC ACID INCREASES THE LD<sub>50</sub> OF SODIUM ARSENITE\* (20)

| NaAsO <sub>2</sub><br>(mmol/kg. s.c.) | DMPS                           | DMSA                           |
|---------------------------------------|--------------------------------|--------------------------------|
|                                       | <u>No. Dead</u><br>No. Started | <u>No. Dead</u><br>No. Started |
| 0.35                                  | 0/12                           | 2/24                           |
| 0.40                                  | 5/24                           | 8/24                           |
| 0.45                                  | 0/12                           | 8/36                           |
| 0.46                                  | 2/12                           | —                              |
| 0.50                                  | 8/24                           | 5/24                           |
| 0.55                                  | 13/24                          | 11/36                          |
| 0.60                                  | 18/24                          | 15/36                          |
| 0.65                                  | —                              | 10/12                          |
| 0.70                                  | 23/24                          | 33/36                          |
| 0.75                                  | —                              | 12/12                          |
| LD <sub>50</sub> (mmol. kg)           | 0.538                          | 0.573                          |
| 95% Confidence interval               | (0.492, 0.590)                 | (0.443, 0.708)                 |

\*DMPS or DMSA, 0.80 mmol. kg. was given, i. p. immediately after and 90 min after NaAsO<sub>2</sub>.

TABLE 7. LD<sub>50</sub> OF DIMERCAPTOPROPANESULFONATE IN MICE (20)

| DMPS<br>(mmols/kg. i. p.)   | <u>Dead</u><br>Started |
|-----------------------------|------------------------|
| 3.3                         | 0/8                    |
| 4.0                         | 0/8                    |
| 5.0                         | 7/16                   |
| 5.5                         | 5/8                    |
| 6.0                         | 7/8                    |
| 6.6                         | 15/16                  |
| 7.0                         | 8/8                    |
| 9.9                         | 8/8                    |
| LD <sub>50</sub> (mmols/kg) | 5.22                   |
| 95% Confidence interval     | (4.35, 5.51)           |

(10) in Japan. An LD<sub>50</sub> in excess of 16.5 mmols/kg has been reported by Friedheim and Corvi (12). It is not clear whether this latter higher value is due to a difference in the mouse strains used or is due to a higher purity of DMSA. When mice were given NaAsO<sub>2</sub> (0.15 mmol/kg) s.c. and 10 min later were treated, i. p., with different amounts of DMPS, the ED<sub>50</sub> was found to be 0.066 mmol/kg (Table 9). The ED<sub>50</sub> under these conditions for DMSA was 0.065 mmol/kg. The therapeutic index for DMPS or DMSA under these conditions

TABLE 8. LD<sub>50</sub> OF MESO-DIMERCAPTOSUCCINIC ACID IN MICE (20)

| DMSA<br>(mmols/kg, i.p.)    | Dead<br>Started |
|-----------------------------|-----------------|
| 6.0                         | 0/32            |
| 12.0                        | 8/32            |
| 13.0                        | 6/12            |
| 14.0                        | 9/12            |
| 16.0                        | 19/24           |
| 18.0                        | 17/20           |
| 24.0                        | 32/32           |
| LD <sub>50</sub> (mmols/kg) | 13.58           |
| 95% Confidence<br>interval  | (11.36, 15.22)  |

TABLE 9. DETERMINATION OF THE ED<sub>50</sub> AND THERAPEUTIC INDEX OF 2,3-DIMERCAPTO-I-PROPANE SULFONIC ACID, NaSALT, AND MESO-DIMERCAPTOSUCCINIC ACID WHEN GIVEN 10 OR 35 MIN AFTER 0.15 mmols NaAsO<sub>2</sub>/kg (20)

| Dimercapto<br>agent        | DMPS<br>+ 10 min  | DMSA<br>+ 10 min  | DMPS<br>+ 35 min  | DMSA<br>+ 35 min  |
|----------------------------|-------------------|-------------------|-------------------|-------------------|
| (mmol/kg, i.p.)            |                   | number surviving  | number started    |                   |
| 0.010                      | —                 | 0/24              | —                 | 0/12              |
| 0.015                      | 0/36              | —                 | 3/36              | —                 |
| 0.030                      | 1/36              | 5/24              | 7/36              | 1/30              |
| 0.040                      | —                 | 6/24              | —                 | —                 |
| 0.045                      | 6/24              | —                 | 8/24              | —                 |
| 0.050                      | —                 | 10/24             | —                 | —                 |
| 0.060                      | 6/24              | 13/24             | 18/24             | 5/38              |
| 0.0675                     | 15/24             | —                 | —                 | —                 |
| 0.070                      | —                 | 9/12              | —                 | —                 |
| 0.075                      | 21/24             | —                 | —                 | —                 |
| 0.080                      | —                 | 18/24             | —                 | 5/12              |
| 0.090                      | 20/24             | —                 | 15/24             | 3/10              |
| 0.100                      | —                 | —                 | —                 | 16/28             |
| 0.105                      | 31/36             | —                 | 30/36             | —                 |
| 0.120                      | 35/36             | —                 | 34/36             | 8/12              |
| 0.125                      | —                 | 21/24             | —                 | 13/17             |
| 0.150                      | —                 | —                 | —                 | 21/30             |
| 0.160                      | —                 | —                 | —                 | 6/8               |
| 0.200                      | —                 | —                 | —                 | 37/46             |
| 0.300                      | —                 | —                 | —                 | 35/38             |
| ED <sub>50</sub> (mmol/kg) | 0.066             | 0.065             | 0.061             | 0.119             |
| Confidence<br>interval     | (0.059-<br>0.072) | (0.040-<br>0.086) | (0.048-<br>0.072) | (0.071-<br>0.164) |
| Therapeutic<br>index       | 79                | 209               | 86                | 115               |

was 79 and 209, respectively. When the DMPS and DMSA was given 35 min after the  $\text{NaAsO}_2$ , the therapeutic index was found to be 86 and 115, respectively. As can be seen under these conditions, DMSA can be considered to be a more effective agent than DMPS in protecting mice against the lethal effects of  $\text{NaAsO}_2$  under these conditions.

Other metal binding agents were also tested for their activity in protecting against the lethal effects of  $\text{NaAsO}_2$ . Neither D-pen nor N-Ac-DL-Pen changes the  $\text{LD}_{50}$  of  $\text{NaAsO}_2$  significantly at the 95% level of significance (Table 10). Other agents (data not shown) that were also found to be ineffective in this respect are the sodium salt of diethyldithiocarbamate,  $\alpha$ -mercaptopropionylglycine, DL-N-acetylhomocysteinethiolactone, and monomercaptosuccinic acid.

TABLE 10. NEITHER D-PENICILLAMINE NOR N-ACETYL-DL-PENICILLAMINE INCREASED THE  $\text{LD}_{50}$  OF SODIUM ARSENITE (20)

|                                      | none                          | D-Pen*                        | N-Ac-DL-Pen*                  |
|--------------------------------------|-------------------------------|-------------------------------|-------------------------------|
| $\text{NaAsO}_2$<br>(mmols/kg, s.c.) | <u>Dead</u><br><u>Started</u> | <u>Dead</u><br><u>Started</u> | <u>Dead</u><br><u>Started</u> |
| 0.10                                 | 0/12                          | 0/8                           | 0/8                           |
| 0.12                                 | 2/12                          | 5/8                           | 1/8                           |
| 0.13                                 | 7/12                          | 7/8                           | 5/8                           |
| 0.14                                 | 12/12                         | 8/8                           | 4/8                           |
| 0.16                                 | 12/12                         | 8/8                           | 8/8                           |
| 0.20                                 | —                             | 8/8                           | 8/8                           |
| $\text{LD}_{50}$ (mmol/kg)           | 0.127                         | 0.119                         | 0.133                         |
| 95% Confidence<br>interval           | (0.080-<br>0.131)             | (0.078-<br>0.191)             | (0.054-<br>0.142)             |

\*D-pen or N-Ac-DL-pen (0.80 mmols/kg) was given, i.p., immediately following and at 90 min after the metal binding agent.

#### *DMPS and DMSA Have Anti-Lewisite Activity*

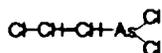
The name British Anti-Lewisite is ingrained very firmly in the mind of most biomedical investigators and physicians. One of the reasons for this is that most medical students and biomedical graduate students are told, in class, at one time or another, of the rational discovery and development of this metal chelating agent as an antidote for lewisite. This almost necessitates that any compound proposed as a replacement of BAL be shown to have anti-lewisite activity. Thus, we have tested DMPS and DMSA for their activity in protecting against the lethal effects of lewisite. The experiments were begun last March in collaboration with Drs. Brennie Hackley, Millard Mershon and Mr. Floyd Brinkley at the BioMed Laboratory at Aberdeen.

Lewisite is an arsenic containing CW agents. It is an oily liquid at 20°. It causes blisters, tissue destruction and blood vessel injury. Systemic poisoning

leading to death is possible. As a CW agent, it is considered to be a moderately delayed casualty agent. Its chemical formula is shown in Figure 2.

Since the introduction of British Anti-Lewisite at the beginning of World War II, all of the therapy of prophylaxis of lewisite has been aimed at chelating the arsenic in the molecule and making it biologically unavailable. This was the basis of Sir Rudolph Peters' search for British Anti-Lewisite.

In the present experiments, the rabbit is anesthetized and then shaved. Using a microliter syringe, lewisite (29.7  $\mu\text{mols/kg}$ ) is injected s.c. The volume of lewisite injected usually amounted to between 7 and 11  $\mu\text{l}$ , depending on the weight of the animal. Table II shows that either DMSA or DMPS will protect rabbits against the lethal effects of lewisite. Using lewisite alone, none of the 6 animals survived. If the animals received 75  $\mu\text{mols/kg}$  at the times indicated, all of the animals survived. DMSA protects against the lethal systemic effects of lewisite. In the second experiment, only 1 of 6 animals receiving lewisite survived; 66% survived when receiving the 75  $\mu\text{mols/kg}$  DMPS regimen; and 50% of those receiving BAL survived. We do not wish to imply that the effectiveness of these agents against lewisite is in the order of  $\text{DMSA} > \text{DMPS} > \text{BAL}$ . More data are needed before relative effectiveness can be stated.



LEWISITE

(2-CHLOROETHENYL)- ARSONOUS DICHLORIDE

FIG. 2. Chemical formula for lewisite.

TABLE II. DMSA OR DMPS WILL PROTECT RABBITS AGAINST LETHAL EFFECTS OF LEWISITE

| Expt. | $\mu\text{mols/kg}^*$ | 7-day survival<br>survival start | %   |
|-------|-----------------------|----------------------------------|-----|
| I     | LEW† —                | 0/6                              | 0   |
|       | LEW + 75 DMSA         | 6/6                              | 100 |
| II    | LEW + —               | 1/6                              | 17  |
|       | LEW + 75 DMPS         | 4/6                              | 66  |
|       | LEW + 75 BAL          | 3/6                              | 50  |

\*All agents were given s.c. except BAL, which was given i.m. The stated amount of dimercapto compounds were given at +1', +90', +180', +360' after lewisite and a.m. and p.m. on day 2 and 3. †29.7  $\mu\text{mols/kg}$  lewisite/kg. These experiments were performed in collaboration with Drs. B. Hackley, M. Mershon and Mr. F. Brinkley.

The data, however, clearly show that DMSA or DMPS will protect rabbits against the lethal effects of lewisite. In this respect the compounds can be said to have Anti-Lewisite activity.

#### *Treatment of Cadmium Toxicity*

Cadmium is virtually ubiquitous. It is deposited and accumulates in most body tissues. It is found in all environmental compartments (air, soil, food and water). The study of cadmium biology has been stimulated by the debilitating osteoporosis of Itai-Itai disease in Japanese adults and the awareness that the increased use of cadmium in industrial and agricultural processes has greatly increased the prevalence of cadmium in the environment (28-30). Along with this, there has been an increased incidence of both acute and chronic cases of clinically identifiable cadmiosis (31). In the U.S., although the cadmium content of the human fetus is about 1  $\mu\text{g}$ , the body burden increases approximately 30,000-fold (to about 30 mg) by age 50 years (32).

In experimental acute cadmium poisoning, DTPA or EDTA are marginally effective (30, 33-37) and dimercaptopropanol is contraindicated (37-39). It is astonishing that no accepted dependable effective drugs have become available for treatment of cadmium intoxication, especially since the biological effects of cadmium have been studied intensively during the last 20 years. Thus a number of research groups have been involved recently in a search for an agent to treat cadmium intoxication (18, 30, 41).

I would like to present in a very brief manner some of the unpublished results of my laboratory group as to attempts to find a therapeutically useful cadmium binding agent. DMPS protects mice against the lethal action of cadmium chloride (Tables 12, 13 and 14). Multiple ligand therapy, however, involving  $\text{CdCl}_2$ , DMPS and EDTA is ineffective. These observations (Tables 13 and 14) confirm those of Planas-Bohne (41) and to some extent those of Jones *et al.* (18).

In Table 14 are summarized the results with penicillamine and its analogs. Under the conditions of these experiments neither penicillamine nor any of its analogs so tested were active in protecting against cadmium lethality. Recent work by Yoshida *et al.* (40) with peptide fragments of mouse metallothionein is encouraging and should be extended to test peptide analogs of metallothionein fragments. Our own results are only a beginning and all studies with cadmium lethality and its therapy should be followed by kidney function tests.

#### *Clinical Effectiveness in Man*

Obviously the results of experiments summarized here and elsewhere warrant the continued investigation of these metal binding agents and their

TABLE 12. DMPS PROTECTS MICE AGAINST LETHAL ACTION OF CADMIUM CHLORIDE BUT MULTIPLE LIGAND THERAPY IS INEFFECTIVE

| Group | CdCl <sub>2</sub><br>(mmol/kg)<br>(i.p.) |   | Chelator(s)<br>(mmol/kg)<br>(i.m.)         | Cumulative 28-day survival<br>No. surviving, No. started | %   |
|-------|--|---|--|--|-----|
| I     | 0.06                                     | + | (saline)                                   | 13/56  | 23  |
| II    | 0.06                                     | + | 1.0 DMPS                                   | 19/20  | 95  |
| III   | 0.06                                     | + | 0.4 DMPS                                   | 12/20  | 60  |
| IV    | 0.06                                     | + | 0.2 DMPS                                   | 6/30   | 20  |
| V     | 0.06                                     | + | 0.50 CaNa <sub>2</sub> EDTA                | 12/18  | 67  |
| VI    | 0.06                                     | + | 0.10 CaNa <sub>2</sub> EDTA                | 8/20   | 40  |
| VII   | 0.06                                     | + | 0.05 CaNa <sub>2</sub> EDTA                | 4/18   | 22  |
| VIII  | 0.06                                     | + | 1.0 DMPS &<br>0.50 CaNa <sub>2</sub> EDTA  | 10/10  | 100 |
| IX    | 0.06                                     | + | 0.40 DMPS &<br>0.10 CaNa <sub>2</sub> EDTA | 2/12   | 17  |
| X     | 0.06                                     | + | 0.20 DMPS &<br>0.10 CaNa <sub>2</sub> EDTA | 3/12   | 25  |
| XI    | 0.06                                     | + | 0.20 DMPS &<br>0.05 CaNa <sub>2</sub> EDTA | 3/10   | 30  |
| XII   | (saline)                                 | + | 1.00 DMPS                                  | 9/10   | 90  |

\*The i.m. injections were given 60 min after the i.p. injection of Cd.

†The one animal that did not survive in this group died on Day 21. Death appeared to be the result of fighting.

‡When saline was given i.p. instead of CdCl<sub>2</sub> and any of the following were given i.m. (mmol/kg) the survival was 100%: DMPS (0.80) or (0.20); CaNa<sub>2</sub>EDTA (0.50) or (0.05); DMPS (1.0) & CaNa<sub>2</sub>EDTA (0.5); DMPS (0.20) & CaNa<sub>2</sub>EDTA (0.05).

TABLE 13. DMPS GIVEN ORALLY INCREASES THE SURVIVAL OF MICE RECEIVING CADMIUM CHLORIDE (0.06 mmol/kg) I.P.

| Group   | Time after CdCl <sub>2</sub> that<br>DMPS (1.0 mmol/kg)*<br>was given orally<br>(min) | Cumulative 28-day survival<br>No. surviving No. started | %   |
|---|---|---|-----|
| I   | -†, -   | 1/16  | 6   |
| II  | +10, +90  | 10/16   | 62  |
| III   | +10, +90  | 13/15   | 87  |
| IV  | - , +90   | 10/16   | 62  |
| The following groups are controls and received saline in place of CdCl <sub>2</sub> |   |   |     |
| V   | +10, -  | 14/16   | 88  |
| VI  | +10, +90  | 16/16   | 100 |
| VII   | - , +90   | 16/16   | 100 |

\*The amount of DMPS given at each time.

†If DMPS was not administered, saline was given in its place.

TABLE 14. NEITHER PENICILLAMINE NOR ITS ANALOGS PROTECT MICE FROM THE LETHAL EFFECTS OF CADMIUM

| Group | CdCl <sub>2</sub><br>(i.p.)<br>(mmol/kg) | Thiol compound<br>(oral)<br>(mmol/kg)* | Min after CdCl <sub>2</sub><br>that thiol compd, | Cumulative<br>28-day survival % |     |
|-------|--|--|--|---------------------------------|-----|
| I     | 0.06                                     | + (saline)                             | —, —, —  | 2/32                            | 6   |
| II    | 0.06                                     | + 1.0 N-Ac-Pen                         | +10, +90, +180                                   | 1/8                             | 13  |
| III   | 0.06                                     | + 1.0 N-Ac-Pen                         | +10, +—, +—                                      | 0/8                             | 0   |
| IV    | (saline)                                 | + 1.0 N-Ac-Pen                         | +10, +90, +180                                   | 8/8                             | 100 |
| V     | 0.06                                     | + 1.0 D-Pen                            | +10, +90, +180                                   | 15/16                           | 94  |
| VI    | 0.06                                     | + 1.0 D-Pen                            | +10, +—, +—                                      | 0/8                             | 0   |
| VII   | 0.06                                     | + 1.0 D-Pen                            | +10, +90, +—                                     | 1/8                             | 12  |
| VIII  | (saline)                                 | + 1.0 D-Pen                            | +10, +—, +—                                      | 8/8                             | 100 |
| IX    | (saline)                                 | + 1.0 D-Pen                            | +10, +90, +—                                     | 7/8                             | 88  |
| X     | (saline)                                 | + 1.0 D-Pen                            | +10, +90, +180                                   | 7/8                             | 88  |
| XI    | 0.06                                     | + 1.5 N-Ac-thiolisoleuc                | +10, +90, +180                                   | 0/8                             | 0   |
| XII   | 0.06                                     | + 1.0 N-Ac-thiolisoleuc                | +10, +90, +180                                   | 3/16                            | 19  |
| XIII  | (saline)                                 | + 1.5 N-Ac-thiolisoleuc                | +10, +90, +180                                   | 6/8                             | 75  |
| XIV   | 0.06                                     | + 1.0 N-Ac-thiolisoleuc                | +10, +—, +—                                      | 6/8                             | 75  |
| XV    | (saline)                                 | + 1.0 B-thiolisoleuc                   | +10, +—, +—                                      | 3/8                             | 38  |
| XVI   | (saline)                                 | + 1.0 B-thiolisoleuc                   | +10, +—, +—                                      | 9/9                             | 100 |

\*Amount given at each stipulated time.

†These results are the sum of 4 separate experiments.

clinical use in the treatment of heavy metal poisoning. There have been recent reports that confirm their effectiveness in human therapy. DMSA was found to be useful in the treatment of a 46 year-old man who ingested 2000 mg of arsenic in a suicide attempt (42). Treatment with 300 mg DMSA every 6 hr p.o. for 3 days caused an increase in the urinary excretion of arsenic with eventual recovery. DMPS has also been effective in human arsenic poisoning (Wager, personal communication). Friedheim *et al.*, (43) in an extension of experiments with experimental animals have reported the effectiveness of DMSA in treating lead poisoning and that it increases the urinary excretion of lead in smelter workers. DMSA was well tolerated and no signs of toxicity were evident. The usefulness of DMPS in the Iraqi mercury disaster has been

TABLE 15. COMPARISON AND SUMMARY OF SOME OF THE INFORMATION ABOUT AND PHARMACOLOGICAL PROPERTIES OF DMPS AND DMSA

| 3-Dimercaptopropane-1-sulfonate, Na salt (DMPS, unithiol, dimaval)   | Meso-2,3-dimercaptosuccinic acid (DMSA, Succimer)  |
|--|--|
| 1. Synthesized in 1950-51 at the Ukrainian Res. Inst. for Health-Chemistry by Petrunkin. Published in 1956 (4).                      | 1. Friedheim, 1954, used Sb-DMSA to increase Sb uptake in schistosomiasis therapy (5). (Intensively studied by mainland Chinese, 1959, for therapy of occupational metal poisoning (11). Primary Soviet investigator since 1965 has been Okomishnikova (50). |
| 2. Crystalline powder, readily soluble in water. Very stable during sterilization and long-term storage.                             | 2. Crystalline powder. Must be brought to pH 5-5.5 before completely soluble in water. Stability during sterilization and long term storage unknown.   |
| 3. Low toxicity, well tolerated even for chronic use, but DMSA is less toxic (20).   | 3. Toxicity is about 2.5 times less than DMPS (20).  |
| 4. Major toxic effect of high dose is hypotension (6, 8).  | 4. Major toxic effect of high dose unknown at present.   |
| 5. Distributed in extracellular space, exclusively (14). Excretion is urinary and rapid (14). Metabolic involvement supposedly none. | 5. Distribution in body compartments unknown at present.   |
| 6. Effective antidote for As, Hg, Sb, Ag, Au, Cu, Cr, Pb, Po, Co, (6, 7, 16, 20, 45-49)  | 6. Effective antidote for As, Pb, Hg, Zn (16, 20, 50-54)   |
| 7. Urinary excretion of Cu and Zn. Increase Fe, Co, Mn or Ni excretion, none or minimal (55).  | 7. Urinary excretion of Co, Fe, Mn, Cu, or Zn, none or minimal (43).   |
| 8. Increase bile flow.   | 8. Effect on bile flow unknown.  |
| 9. Therapeutic dose about 250 mg for 70 kg man.  | 9. Therapeutic dose from 0.5 to 2 g for 70 kg man.   |
| 9. Can be given by mouth, s.c., i.p., i.m., i.v. Only 30-40% of oral dose absorbed from g.i. tract.                                  | 10. Can be given by mouth, s.c., i.p., i.m., i.v. Indications of oral dose being completely absorbed from g.i. tract.  |

documented recently (44). In fact DMPS, as DIMAVAL, is an approved drug in West Germany for the treatment of mercury poisoning.

There are many reports in the Soviet literature dealing with DMPS and DMSA both in experimental conditions or for human therapy. Some of them are cited in the summary of the properties of these two very important metal binding agents listed in Table 15. Obviously, these two water soluble analogs of BAL that are advantageous as to overall effectiveness and low toxicity can be expected to replace virtually all the therapeutic uses of British Anti-Lewisite.

#### SUMMARY

Water soluble analogs of British Anti-Lewisite that are active orally and less toxic than BAL are now available. These agents are 2,3-dimercapto-1-propanesulfonic acid and meso-dimercaptosuccinic acid. Evidence for their effectiveness in preventing the lethal effects of sodium arsenite in mice and lewisite in rabbits is presented. These analogs can be expected to replace BAL in the treatment of heavy metal poisoning.

#### ACKNOWLEDGEMENTS

The author wishes to express his sincere appreciation to Mrs. Linda Boxhorn for her responsible and thoughtful technical assistance and to Heyl and Co. for supplying the DMPS (DIMAVAL). This work was supported by contract DAMD17-80-C-0052 from the USAMRDC. Much of the work reported from the author's laboratory has been published (16, 20).

#### REFERENCES

1. C. D. KLAASEN, Heavy metals and heavy-metal antagonists, pp. 1615-1637 in *The Pharmacological Basis of Therapeutics* (A. G. GILMAN, L. S. GOODMAN and A. GILMAN, eds.), Macmillan, New York (1980).
2. J. M. WALSHE, Penicillamine, a new oral therapy for Wilson's disease, *Am. J. Med.* 21, 487-495 (1956).
3. H. V. APOSHIAN and M. M. APOSHIAN, N-acetyl-DL-penicillamine, a new oral protective agent against the lethal effects of mercuric chloride, *J. Pharmacol. Exptl. Ther.* 126, 131-135 (1959).
4. V. E. PETRUNKIN, Synthesis and properties of dimercapto derivatives of alkylsulfonic acids. *Ukr. Khim Zhurn.* 22, 603-607 (1956).
5. E. FRIEDHEIM, J. R. DASILVA, and A. V. MARTINS, Treatment of Schistosomiasis Mansoni with antimony a-dimercapto-potassium succinate (TWSb), *Am. J. Trop. Med. Hyg.* 3, 714-727 (1954).
6. S. I. ASHBEL, Unithiol in prophylaxis and therapy of occupation conditioned poisoning with mercury and its organic compounds, pp. 161-168 in *Tiologvye soyedineniya v meditsine* (N. N. LUGANSKIY, V. E. PETRUNKIN, P. V. RODIONOV and A. J. CHERKES, eds.), Kiev: Gos. Med. Izd. Ukrain, SSR. (1959).
7. G. A. BELONOZYKO, Therapeutic action of unithiol in poisoning with inorganic mercury compounds, *Farmakol. i Toksikol.* 21, 69-73 (1958).

8. L. K. KLIMOVA, Materially k farmakologii unitiola. pp. 135-138 in *Tiolyve soyedineniya v meditsine* (N. N. LUGANSKIY, V. E. PETRUNKIN, P. V. RODIONOV and A. J. CHERKES eds. Gos. Med. Izd. Ukrain. SSR, Kiev (1959).
9. N. M. KOSTYGOV, The antidotal action of mercaptosuccinic acid and Unithiol against mercury, *Farmakol. i. Toksikol.* 21, 64-69 (1958).
10. Y. MATSUDA, Experimental study on sodium dimercaptosuccinic acid, *Gifu Daigaku Igakubu Kiyo* 1, 869-888 (1968).
11. W. SHIH-CHUN, T. KUANG-SHENG and W. CHIH-CHUNG, Chelating therapy with NaDMS in occupational lead and mercury intoxication, *Chin. Med. J.* 84, 437-439 (1965).
12. E. FRIEDHEIM and C. CORVI, Meso-dimercaptosuccinic acid, a chelating agent for the treatment of mercury poisoning, *J. Pharm. Pharmacol.* 27, 624-626 (1965).
13. B. GABARD, Treatment of methylmercury poisoning in the rat with sodium 2,3-dimercaptopropane-1-sulfonate: Influence of dose and mode of administration, *Toxicol. appl. Pharmacol.* 38, 415-424 (1976).
14. B. GABARD, Distribution and excretion of the mercury chelating agent sodium 2,3-dimercaptopropane-1-sulfonate in the rat, *Arch. Toxicol.* 39, 289-298 (1978).
15. G. C. BATTISTONE, R. A. MILLER and M. RUBIN, The use of 2,3-dimercapto-propane sodium sulfonate (DMPS) in mercury chelation therapy, pp. 221-224 in *Clinical Chemistry and Chemical Toxicology of Metals* (S. S. BROWN, ed.) Elsevier Press, (1977).
16. C. H. TADLOCK and H. V. APOSHIAN, Protection of mice against the lethal effects of sodium arsenite by 2,3 dimercapto-1-propane-sulfonic acid and dimercaptosuccinic acid, *Biochem. Biophys. Res. Commun.* 94, 501-507 (1980).
17. W. HAUSER and N. WEGER, Treatment of arsenic poisoning in mice with sodium dimercapto-1-sulfonate, *7th Internat. Cong. Pharmacol.* Paris, (1978).
18. M. M. JONES, A. D. WEAVER, and W. L. WELLER, The relative effectiveness of some chelating agents as antidotes in acute cadmium poisoning, *Res. Commun. Path. and Pharmacol.* 22, 581-588 (1978).
19. M. M. JONES and M. A. BASINGER, Comparison of standard chelating agents for acute mercuric chloride poisoning in mice, *Res. Commun. Chem. Path. and Pharmacol.* 24, 525-531 (1979).
20. H. V. APOSHIAN, C. H. TADLOCK and T. E. MOON, Protection of mice against the lethal effects of sodium arsenite — A quantitative comparison of a number of chelating agents, *Toxicol. Appl. Pharmacol. (in Press)* (1981).
21. A. CATSCH and A. E. MARMUTH-HOENE, Pharmacology and therapeutic applications of agents used in heavy metal poisoning, pp. 107-224 in *The Chelation of Heavy Metals* (W. G. LEVINE, ed.) Pergamon, Oxford (1979).
22. W. I. DIXON and M. B. BROWN, *Biomedical Computer Program P-Series*, Univ. California Press, Los Angeles (1979).
23. D. J. FINNEY, *Experimental Design and Analysis of Experiments*, The University of Chicago Press, Chicago (1955).
24. R. G. PETERSON and B. H. RUMACH, D-Penicillamine therapy of acute arsenic poisoning, *J. Pediatr.* 91, 661-666 (1977).
25. J. ST. PETERY, O. M. RENNERT, H. CHOI and S. WOLFSON, Arsenic poisoning in childhood, *Clin. Toxicol.* 3, 519-526 (1970).
26. A. KURUVILLA, P. S. BERGESON and A. K. DONE, Arsenic poisoning in childhood — an unusual case report with special notes on therapy with penicillamine, *Clin. Toxicol.* 8, 535-540 (1975).
27. F. PLANAS-BOHNE, B. GABARD and E. H. SCHAFFER, Toxicological studies on sodium 2,3-dimercaptopropane-1-sulfonate in the rat, *Arzeim.-Forsche. Drug Res.* 30, 1291-1294 (1980).
28. *Health Assessment Document for Cadmium*, U.S. Environmental Protection Agency, Washington, D.C., May (1978).
29. *Atmospheric Cadmium: Population Exposure Analysis*, U.S. Environmental Protection Agency, Washington, D.C., March (1978).

30. L. FRIBERG, M. PISCATOR, G. NORDBERG and T. KJELLSTROM, *Cadmium in the Environment*, 2nd Edition. CRC Press, Cleveland, OH (1974).
31. D. F. FLICK, H. F. KHAYBILL and J. M. DIMITROFF, Toxic effects of cadmium: A review. *Environmental Research* 4, 71-85 (1971).
32. M. WEBB and M. DANIEL, Induced synthesis of metallothionein by pig kidney cells *in vitro* in response to cadmium, *Chem. Biol. Interact.* 10, 269-276 (1975).
33. A. CATSCH and A. E. HARMUTH-HOENE, New developments in metal antidotal properties of chelating agents. *Biochem. Pharmacol.* 24, 1557-1562 (1975).
34. D. W. FASSETI, Cadmium: Biological effects and occurrence in the environment. *Ann. Rev. Pharmacol.* 15, 425-435 (1975).
35. L. FRIBERG, M. PISCATOR and C. NORDBERG, *Cadmium in the Environment*. CRC Press, Cleveland, OH (1972).
36. V. EYBL, J. SYKORA and F. MERTL, Effect of CaEDTA and CaDTPA in cadmium intoxication, *Acta biol. med. germ.* 17, 178-185 (1966).
37. B. NIEMEIR, Der einfluss von chelatbildnern auf verteilung und Toxicitat von cadmium, *Int. Arch. Gewerbepath.* 24, 160-168 (1967).
38. J. SCHUBERT, Heavy metals — toxicity and environmental pollution, pp. 239-297 in *Experimental Medicine & Biology*, 40, (S. K. DHAR, ed.), Plenum, New York (1973).
39. R. BERKOW and J. H. TALBOTT, (eds.), *The Merck Manual of Diagnosis and Therapy*, 1974-1981 (Merck Sharp and Dohme Research Laboratories, Rahway, 1977).
40. A. YOSHIDA, B. E. KAPLAN and M. KIMURA, Metal-binding and detoxification effect of synthetic oligopeptides containing three cysteinyl residues, *Proc. Natl. Acad. Sci. U.S.A.* 76, 486-490 (1979).
41. F. PLANAS-BOHNE, Chelate treatment in acute cadmium poisoning. *Experientia* 35, 8-9 (1980).
42. K. LENZ, K. HRUBY, W. DRUML, A. EDER, A. GASZNER, G. KLEINBERGER, M. PICHLER and M. WEISER, 2,3-dimercaptosuccinic acid in human arsenic poisoning. *Arch. Toxicol.* 47, 241-243 (1981).
43. E. FRIEDHEIM, J. H. GRAZIANO, D. POPOVAC, D. DRAGOVIC and B. KUAL, Treatment of lead poisoning by 2,3-dimercaptosuccinic acid, *Lancet* ii, 1234-1235 (1978).
44. T. W. CLARKSON, L. MAGOS, C. COX, M. R. GREENWOOD, L. AMIN-ZAKI, M. A. MAJEED and S. F. AL-DAMLUSI, Test efficacy of antidotes for removal of methylmercury in human poisoning during the Iraq outbreak, *J. Pharmacol. Exptl. Therap.* 248, 74-83 (1981).
45. S. S. ROMANOV, Unithiol as an antidote in pulmonary edema secondary to intravenous injection of silver nitrate, *Farmakol. Toksikol.* 30, 237-238 (1967).
46. E. ANGELOVA and T. STOYTCHEV, Experimental studies on the antidotal and copper-decorporating effects of Unithiol upon acute poisoning with copper sulfate and the influence of acidoses and alkaloses on these effects, *Bulgarian Acad. Sci.* 15, 179-186 (1973).
47. A. A. SARKISIAN, G. A. EPREMIAN and P. S. SIMAVORIAN, Biochemical and morphologic changes in kidneys in chromium poisoning and therapeutic effectiveness of unithiol. *Zhurnal Eksperimentalnoi i Klinicheskoi Meditsiny.* 11, 25-31 (1971).
48. M. G. ZOTOVA, Effect of unitol on the elimination of  $Po^{210}$ , *Med. Radiologiya* 3, 67-68 (1958).
49. A. I. CHERKES and B. S. BRAVER-CHERNOBULSKAYA, Unithiol — A cobalt antidote, *Farmakol. i Toksikol. (Moscow)*, 21, 59-63 (1958).
50. I. Y. OKONISHNIKOVA, Experimental therapy and prophylaxis of acute poisoning with arsenic compounds. *Gig. Tr. Prof. Zabol.* 9, 38-43 (1965).
51. I. Y. OKONISHNIKOVA, E. E. ROZENBERG and I. A. REZINA, The therapeutic-prophylactic effect of succimer in experimental subacute lead acetate poisoning, *Gig. Tr. Prof. Zabol.* 8, 24-28 (1976).
52. J. H. GRAZIANO, D. CUCCIA and E. FRIEDHEIM, The pharmacology of 2,3-dimercaptosuccinic acid and its potential use in arsenic poisoning, *J. Pharmacol. Exptl. Therap.* 207, 1051-1055 (1978).

53. L. MAGOS, The effects of dimercaptosuccinic acid on the excretion and distribution of mercury in rats and mice treated with mercuric chloride and methyl-mercury chloride, *Brit. J. Pharmacol.* **56**, 479-484 (1976).
54. J. AASETH and E. A. H. FRIEDHEIM, Treatment of methyl mercury poisoning in mice with 2,3-dimercaptosuccinic acid and other complexing thiols, *Acta Pharmacol. et Toxicol.* **42**, 248-252 (1978).
55. B. GABARD, F. PLANAS-BOHNE and G. REGULI, The excretion of trace elements in rat urine after treatment with 2,3-dimercaptopropane sodium sulfonate, *Toxicology* **12**, 281-284 (1979).

**NOTICE**  
**THIS MATERIAL MAY BE PROTECTED BY**  
**COPYRIGHT LAW (TITLE 17, U.S. CODE)**

Reprinted with permission  
through the Copyright  
Clearance Center

**ANTI-LEWISITE ACTIVITY AND STABILITY OF MESO-DIMERCAPTOSUCCINIC  
ACID AND 2,3-DIMERCAPTO-1-PROPANESULFONIC ACID**

H.V. Aposhian, M. M. Mershon\*, F. B. Brinkley\*, Chin-An Hsu,  
and B. E. Hackley\*

Department of Cellular and Developmental Biology, University  
of Arizona, Tucson, AZ 85721; and USAMRICD, Aberdeen, MD 21010

(Received in final form August 9, 1982)

Summary

Meso-dimercaptosuccinic acid (DMSA) and the sodium salt of 2,3-dimercapto-1-propanesulfonic acid (DMPS) are analogous in chemical structure to dimercaprol (BAL, British Anti-Lewisite). Dimercaprol was among the first therapeutically useful metal chelating agents and was developed originally as an anti-lewisite agent. Either DMSA or DMPS protects rabbits from the lethal systemic action of dichloro(2-chlorovinyl)arsine (29.7  $\mu$ moles/kg, also known as lewisite. The analogs are active in this respect when given either sc or po. The stability of each of the three dimercapto compounds in distilled H<sub>2</sub>O, pH 7.0 at 24°, has been examined for seven days. DMSA retained 82% of its mercapto groups, but no titratable mercapto groups remained in the DMPS or BAL solutions. At pH 5.0, however, there was no striking difference in the stability of the three dimercapto compounds (78-87%) over a seven day period. DMSA and DMPS warrant further investigation as water soluble metal binding agents in both in vivo and in vitro experiments.

British Anti-Lewisite (BAL, dimercaprol) was developed in the 1940's as an antidote to dichloro-(2-chlorovinyl)-arsine, commonly called lewisite (1,2). The lethal action of lewisite is believed to be the result of its combining with one or more sulfhydryl groups and thus inactivating essential sulfhydryl-containing enzymes (3). It is the arsenic in the lewisite molecule that reacts with sulfhydryl moieties.

At the time of its introduction into clinical medicine, BAL was considered by many to be the long sought, universal antidote for heavy metal poisoning. In subsequent years, however, less toxic and more specific metal binding agents have been sought and investigated. Some have met the criteria and standards necessary for clinical use. Others have not. For example, BAL glucoside was introduced (4) as a result of a search for water soluble and less toxic analogs of BAL. Although it was found to be less toxic than BAL for iv use, (probably because of its low lipid solubility), it did not become established as a clinical agent because it is unstable chemically. Other compounds, which are less analogous in chemical structure, have replaced BAL for some of its more specific therapeutic uses. For example, D-penicillamine is used to mobilize and increase the excretion of copper in patients with Wilson's Disease (5). Its N-acetyl derivative is effective as a mercury antidote (6,7). BAL has remained, however, the drug of choice in the U.S. for the treatment of arsenic poisoning.

Meso-dimercaptosuccinic acid (DMSA) (8) and the sodium salt of 2,3-dimercapto-1-propanesulfonic acid (DMPS) (9) are promising replacements for BAL. These compounds are very similar in chemical structure to BAL and are sometimes referred to as water soluble and/or orally-effective analogs of BAL. To our knowledge, however, the anti-lewisite activity of these two important chemical analogs has not been determined. Neither are any published data available concerning the stability of aqueous solutions of these dimercapto compounds. Evidence for the anti-lewisite activity and stability of DMPS and DMSA are presented in this paper.

#### Materials and Methods

Male New Zealand white stock rabbits weighing 2.5-3.5 kg were purchased from Dutchland Laboratories Inc., Denver, PA and Davidson Mill Farm, Jonesburg, NJ and caged individually. Food (Purina Rabbit Chow Brand 5322) and water were available ad libitum except in the case of those animals who received therapy orally. Animals receiving therapy po were fasted from 16 hrs prior to the first administration to 1 hr after the last administration on day one. On days two and three, animals were fasted from 1 hr prior to the morning administration to 1 hr after the evening administration, approximately 7 hours.

When dithiol therapy was given sc, the animals were anesthetized fifteen minutes before lewisite administration by administering im 0.50 ml of anesthetic solution per kg. The animals were anesthetized to reduce the pain expected to be caused by lewisite. Subsequently, it was observed that neither pain nor discomfort was apparent. Thus, anesthesia was not used in the experiments when dithiols were given po. The anesthetic solution was prepared by mixing 5 parts Ketamine HCl (100 mg/ml) and 1 part of Xylazine (100 mg/ml).

A 5 ml Gilson Pipetman was used to give the dithiols by mouth. The rabbit was placed in a short restraining box. The box was placed on its end so that the rabbit was in a vertical position with its head at the top. The Pipetman was filled with the desired volume of the drug solution. The plastic tip was gently inserted between the lips at one corner of the mouth and the liquid delivered slowly into the back of the rabbit's mouth. This method did not appear to cause any trauma or injury. It was easier and faster to perform than the use of polyethylene stomach tubes.

NaDMPS was a gift of Heyl and Co., Berlin. Since each molecule has a molecule of H<sub>2</sub>O associated with it, a molecular weight of 228.2 was used in calculations. DMSA was a gift of Johnson and Johnson, Skillman, N.J. Both compounds were pharmaceutical grade purity. DMPS and DMSA were titrated with iodine in order to measure purity and mercapto content. By this criterion, each preparation was judged to be greater than 99% pure. The compounds when given by mouth were dissolved in water. In order to dissolve DMSA, the aqueous suspension was adjusted to pH 5.5 with NaOH. When given sc, the solutions were prepared the same way except that the compounds were dissolved in 0.9% NaCl-5% NaHCO<sub>3</sub>. Unless otherwise stated, the concentrations of DMPS or DMSA were such that the rabbit received 1.0 ml of solution per kg of body weight, per administration. Dimercaprol Injection, USP (BAL in Oil Ampules) was a gift of Hynson, Wescott & Dunning, Baltimore, MD.

Lewisite was 97-99.6% pure as judged by NMR-spectroscopy as well as by iodine titration. Analysis by the former method also indicated that the forms of lewisite that were present were trans (97.7%), cis (1.7%) and dimers (0.5%). Lewisite is a hazardous material with which to work since it is a potent vesicant. All handling of lewisite was done in an extremely well

TABLE I

The Anti-Lewisite Activity of Meso-Dimercaptosuccinic Acid and 2,3,-Dimercapto-1-Propanesulfonate when given sc to rabbits

| Group | $\mu\text{mols/kg}$          | survive/start <sup>a</sup> | % survival |
|-------|------------------------------|----------------------------|------------|
| 1     | LEW <sup>b</sup> + -----     | 1/18                       | 6          |
| 2     | LEW + 75.0 DMSA <sup>c</sup> | 12/12                      | 100        |
| 3     | LEW + 37.5 DMSA              | 6/6                        | 100        |
| 4     | LEW + 20.0 DMSA              | 6/6                        | 100        |
| 5     | LEW + 10.0 DMSA              | 1/6                        | 17         |
| ----- |                              |                            |            |
| 6     | LEW + 75.0 DMPS <sup>c</sup> | 10/12                      | 83         |
| 7     | LEW + 37.5 DMPS              | 5/6                        | 83         |
| ----- |                              |                            |            |
| 8     | LEW + 75.0 BAL <sup>c</sup>  | 8/12                       | 67         |
| 9     | LEW + 37.5 BAL               | 3/6                        | 50         |

<sup>a</sup> In the tables of this paper, the data represent the combined results of a number of separate experiments. This was done to save space. The reason for the number of animals in some groups differing from the number in other groups of the same table is that very often the combined data are the result of from 2-3 separate experiments. Otherwise, the experiments were performed under identical conditions. The survival recorded in this table is that for 7 days after lewisite administration.

<sup>b</sup> Lewisite (29.7  $\mu\text{mols/kg}$ ) was given sc at time zero.

<sup>c</sup> All agents given sc except BAL, which was given im. Dimercapto compounds given at +1 min, +90 min, +180 min, +360 min after lewisite and at 8 a.m. and 4 p.m. on day 2 and 3. Administration of these amounts of dimercapto compound at the times cited above did not cause any fatalities in control animals that did not receive lewisite (data not shown).

<sup>d</sup> Pair-wise comparisons:  $p < 0.0001$  for 1 vs 2;  $p = 0.0001$  for 1 vs 3 and 1 vs 4;  $p < 0.001$  for 1 vs 6 and 1 vs 7;  $p = 0.001$  for 1 vs 8 and 0.01 for 1 vs 9.

vented chemical exhaust hood. Safety glasses and thick neoprene gloves were worn.

The stability of DMPS, DMSA or BAL was determined using iodometric titration. To 2.50 ml of a 0.10 M dimercapto solution, 10 drops of starch indicator solution were added. The solution was titrated using 0.025 N iodine solution until the blue color appeared and persisted for at least 10 sec.

## Results

### Anti-Lewisite Activity

The data of Table 1 clearly show that both DMSA and DMPS have anti-lewisite activity when given subcutaneously. As little as 20  $\mu\text{mol}$ s/DMSA/kg administered sc, according to the stated regimen, protects against the lethal actions of lewisite. Thus, DMSA and DMPS are analogous to BAL not only in chemical structure but also with respect to anti-lewisite activity. In addition, DMSA and DMPS have anti-lewisite activity when given orally (Table 2).

TABLE II

Meso-Dimercaptosuccinic Acid or 2,3-Dimercapto-1-Propanesulfonate is effective, when given by mouth, in protecting rabbits against the lethal effects of Lewisite

| Group | $\mu\text{mol}$ s/kg        | survive/start | % survival |
|-------|-----------------------------|---------------|------------|
| 1     | LEW <sup>a</sup> + -----    | 0/12          | 0          |
| 2     | LEW + 400 DMSA <sup>b</sup> | 5/6           | 83         |
| 3     | LEW + 200 DMSA <sup>b</sup> | 4/6           | 67         |
| 4     | LEW + 400 DMPS <sup>b</sup> | 6/6           | 100        |
| 5     | LEW + 200 DMPS <sup>b</sup> | 4/6           | 67         |
| ----- |                             |               |            |
| 6     | LEW + -----                 | 1/6           | 17         |
| 7     | LEW + DMSA <sup>c</sup>     | 4/6           | 67         |
| 8     | LEW + DMPS <sup>c</sup>     | 1/6           | 17         |

<sup>a</sup> Lewisite (29.7  $\mu\text{mol}$ s/kg) was given sc at time zero.

<sup>b</sup> Dimercapto compounds given po at -45, -2, +90 and +300 min. after lewisite and 8 a.m. and 4 p.m. on day 2 and 3. No fatalities occurred in control animals that received these amount of dimercapto compound, po, (but no lewisite) at the times cited above. Survival was followed and recorded for 7 days after lewisite administration.

<sup>c</sup> Dimercapto compounds given po as follows: 400  $\mu\text{mol}$ s of dimercapto compound /kg at 5 min before lewisite, and 200  $\mu\text{mol}$ s/kg at each of the following times after lewisite: 1 hr., 2.5 hrs. and 5 hrs. on the first day plus 8 a.m. and 4 p.m. on day 2 and 3.

<sup>d</sup> For pair-wise comparison:  $p = 0.001$  for 1 vs 2;  $p = 0.01$  for 1 vs 3;  $p < 0.001$  for 1 vs 4 and  $p = 0.01$  for 1 vs 5

Additional studies have demonstrated that a single po administration of DMSA (400  $\mu\text{mol}$ s/kg) 15 min prior to lewisite was ineffective since only 1 of 6 animals survived for 7 days. In the experiments of Table 1 and 2, most of the rabbits that received lewisite and no dimercapto therapy died within 12 hrs. If animals died after receiving lewisite plus dimercapto therapy, they usually died between the first and fifth day of the experiment.

### Stability Studies

The stabilities of DMSA, DMPS and BAL in 0.10M solutions at pH 5.0 and 7.0 were examined (Fig 1). The mercapto groups of these compounds, in aqueous solutions at pH 5.0, are stable (Fig 1). Even after 7 days at room temperature, from 78 to 87% of the mercapto groups remain titratable. At pH 7.0, however, the greater stability of DMSA is evident with 82% of the mercapto groups remaining after 7 days.

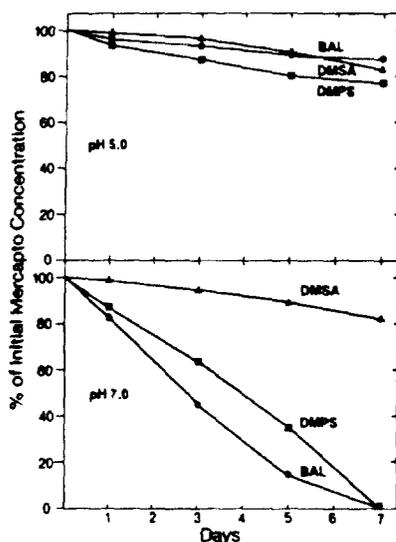


FIG. 1

Stability of DMSA, DMPS and BAL at pH 5.0 or 7.0. Aqueous solutions of each compound were prepared, adjusted to pH 5.0 or 7.0 and to a final concentration of 0.10mmol/ml. Solutions were prepared using double-distilled H<sub>2</sub>O and maintained at 24°. Aliquots were removed at indicated times and the mercapto content determined. Each value shown is the average of two separate titrations.

By this time and under these conditions none of the mercapto groups of DMPS or BAL remained. Other studies (data not shown) indicated that DMSA, in a solution of 5% NaHCO<sub>3</sub>, when either frozen for 4 days or frozen and thawed each day for 4 days retained 82% of its original mercapto groups. If similar solutions were held at 4° or 24° for 4 days, DMSA retained 76% and 69% of its mercapto groups, respectively. Although solutions of DMPS in 5% NaHCO<sub>3</sub> were stable (92-95% of original) when either frozen, or frozen and thawed each day for 7 days, after three days at room temperature no titratable mercapto groups were evident.

### Discussion

Extensive clinical experience with DMSA and DMPS as antidotes and prophylactics for mercury, lead, arsenic and other heavy metals has been

reported in Soviet and mainland Chinese literature (10,11,12,13). In the Soviet Union, DMPS has been for many years an official drug called Unithiol. Recently, there has been a great deal of interest in both of these water soluble chemical analogs of dimercaprol in the United States and abroad (14,15,16,17,18). This has resulted in the confirmation and extension (19,20,21,22) of earlier reports dealing with both the basic and clinical investigations of DMSA and DMPS.

Although dimercaprol is a name relatively easily identified in the field of therapeutics, the compound is known most commonly in other areas as British Anti-Lewisite. It seemed reasonable to expect that a true analog agonist might also have Anti-Lewisite Activity.

The present experiments clearly show that either DMSA or DMPS will protect rabbits against the lethal systemic effects of subcutaneously administered lewisite (Table 1 and 2). Therefore, DMSA and DMPS can be considered to be not only analogous in chemical structure but also in anti-lewisite activity. In addition, DMSA and DMPS are effective when given by mouth; a route not recommended for BAL administration.

The dose schedule for administering DMSA and DMPS was based on a three day regimen recommended in the literature for the use of these metal binding agents. Subsequent studies (Aposhian, unpublished) have demonstrated that as little as one dose of 40  $\mu$ moles/kg of either drug given in one minute after lewisite will result in the survival of 4 out of 6 rabbits. In addition when DMSA therapy is delayed until 90 min after lewisite, 6 of 6 rabbits, survived. The purpose of these studies was to determine whether DMSA or DMPS have anti-lewisite activity. No attempt has been made to quantitate their relative efficacy against lewisite.

Not only are these analogs crystalline and readily water soluble, they are less toxic than BAL. The results of a number of different investigations in rodents have led to the conclusion that the acute toxicity of DMSA is less than that of DMPS which is much less than that of BAL (19,23,24,25).

The stability studies (Fig 1) were initiated for two reasons. Many investigators believe that DMSA and DMPS are unstable because of their dimercapto structure. Since solutions of these compounds were being used throughout the day, for example see Table 1 and 2, it has been considered necessary by a number of investigators (17,20) to prepare solutions immediately before use. The stability of solutions of these dimercapto compounds is somewhat surprising since mercapto compounds are usually thought to be readily oxidized.

In addition to many older reports in the Soviet and Chinese literature (10,12,26) dealing with DMPS and DMSA in human therapy, such use has been strengthened by recent papers containing data from clinical investigations. For example, DMSA has been used recently in the treatment of a 46 yr. old man who ingested 2000 mg of arsenic in a suicide attempt (27). Treatment with 300 mg of DMSA every 6 hrs po for 3 days caused an increase in the urinary excretion of arsenic and eventual recovery. DMSA increased the excretion of lead in the urine of smelter workers and was effective in treating the signs and symptoms of lead poisoning (28). The dimercapto compound was well tolerated and no signs of toxicity were evident. The usefulness of DMPS and other metal binding agents in the treatment of mercury intoxication resulting from the Iraqi mercury disaster has been documented recently (18). DMPS, as DIMAVAL, is now an approved drug in West Germany for the treatment of mercury poison. These two water soluble analogs of BAL, analogous in activity as well

as chemical structure, active when given by mouth and of low toxicity, warrant continued investigation as possible replacements for BAL.

#### Acknowledgements

The authors wish to express their sincere appreciation to Mrs. Linda Boxhorn for her excellent technical assistance; to Heyl and Co. for supplying the DMPS (DIMAVAL<sup>R</sup>); and to Johnson and Johnson for the gifts of DMSA. One of the authors (C.A.H.) was the recipient of a Heyl & Co. postdoctoral fellowship. The assays for lewisite purity were performed by Linda Szafraniec and Paul M. Davis. The authors are indebted to Dr. Thomas E. Moon of the University of Arizona Cancer Center Division for statistical analysis. This work was supported by contract DAMD17-8-C-0052 from the USAMRDC.

#### References

1. R.A. PETERS, L.A. STOCKEN, and R.H.S. THOMPSON, *Nature* 156 616-619 (1945).
2. L.L. WATERS and C. STOCK, *Science* 102 601-606 (1945).
3. L.A. STOCKEN, and R.H.S. THOMPSON, *Physiol. Rev.* 29 168-192 (1949).
4. J.F. DANIELLI, M. DANIELLI, J.B. FRASER, P.D. MITCHEL, L.N. OWEN, and G. SHAW, *Biochem. J.* 41 325-333 (1947).
5. J.M. WALSH, *Amer. J. Med.* 21 487-495 (1956).
6. H.V. APOSHIAN and M.M. APOSHIAN, *J. Pharmacol. Exp. Ther.* 126 131-135 (1959).
7. R.A.P. KARK, D.C. POSKANZER, J.D. BULLOCK, and G. BOYLEN, *N. Engl. J. Med.*, 285 10-16 (1971).
8. E. FRIEDHEIM, J.R. DaSILVA, and A.V. MARTINS, *Amer. J. Trop. Med. Hyg.* 3 714-727 (1954).
9. V.E. PETRUNKIN, *Ukr. Khim. Zh.* 22 603-607 (1956).
10. S.I. ASHBEL, In *Tiоловые soyedineniya v meditsine* (N. N. Luganskiy, V.E. Petrunkin, P. V. Rodionov and A. J. Cherkas, eds.) pp. 161-168. Gos. Med. Izd. Ukrain, SSR, Kiev (1959).
11. L.K. KLIMOVA, *Farmakol. Toksikol.* 21 53-59 (1958).
12. W. SHIH-CHUM, T. KUANG-SHENG, and W. CHIH-CHUNG, *Chin. Med. J.* 84 437-439 (1965).
13. I.Y. OKONISHNIKOVA, *Gig. Tr. Prof. Zabol* 9 38-43 (1965).
14. E. FRIEDHEIM, and C. CORVI, *J. Pharm. Pharmacol.* 27 624-626 (1975).
15. G.C. BATTISTONE, R.A. MILLER, and M. RUBIN, In *Clinical Chemistry and Chemical Toxicology of Metals* (S. S. Brown, ed.) 221-224. Elsevier Press (1977).
16. W. HAUSER, and N. WEGER, In 7th International Congress of Pharmacology. Paris (J. R. Boissier et al., eds.). Pergamon, Elmsford, N.Y (1978).
17. C.H. TADLOCK, and H.V. APOSHIAN, *Biochem. Biophys. Res. Comm.* 94 501-507 (1980).
18. T.W. CLARKSON, L. MAGOS, C. COX, M.R. GREENWOOD, L. AMIN-ZAKI, M.A. MAJEED, and S.F. AL-DAMLUSI, *J. Pharmacol. Expt. Therap.* 248 74-83 (1981).
19. H.V. APOSHIAN, C.H. TADLOCK, and T.E. MOON, *Toxicol. Appl. Pharmacol.* 61 385-392 (1981).
20. M.M. JONES, M.A. BASINGER, A.D. WEAVER, C.M. DAVIS, and W.K. VAUGHN, *Res. Commun. Chem. Pathol. Pharmacol.* 27 363-372 (1980).
21. J.H. GRAZIANO, D. CUCCIA, and E. FRIEDHEIM, *J. Pharmacol. Expt. Therap.* 207 1051-1055 (1978).
22. A. TAYLOR, R.L. LALLONE, *J. Nucl. Med.* 21 1190-1193 (1980).
23. F. PLANAS-BOHNE, B. GABARD, and E.H. SCHAEFFER, *Arzneim.-Forsch.* 30, 8 1291-1294 (1980).
24. L. SZINICZ, W. HAUSER, U. HELL, and N. WEGER, (Drug Research, In Press).

25. P. ZVIRBLIS, and R.I. ELLIN, *Toxicol. Appl. Pharmacol.* 36 397-399 (1976).
26. D.M. ZISLIN, I.E. OKONISHNIKOVA, G.N. SAMOKHVALOVA, and A.S. VORONTSOVA, *Gig. Tr. Prof. Zabol* 12 17-21 (1968).
27. K. LENZ, K. HRUBY, W. DRUMML, A. EDER, A. GASZNER, G. KLEINBERGER, M. PICHLER, and M. WEISER. *Arch. Toxicol.* 47 241-243 (1981).
28. E. FRIEDHEIM, J.H. GRAZIANO, D. POPOVAC, D. DRAGOVIC, and B. KAUL, *Lancet* II, 1234-1235 (1978).

**A. INGREDIENT NAME:**

**FERRIC SUBSULFATE SOLUTION**

**B. Chemical Name:**

**C. Common Name:**

Monsel's Solution, Basic Solution, Iron Hydroxide Sulfate

**D. Chemical grade or description of the strength, quality, and purity of the ingredient:**

|       | <i>(Specification)</i> | <i>(Result)</i> |
|-------|------------------------|-----------------|
| Assay | 20-22%                 | 21.2%           |

**E. Information about how the ingredient is supplied:**

Reddish-Brown liquid, almost odorless, sour, strongly astringent taste, affected by light.

**F. Information about recognition of the substance in foreign pharmacopeias:**

NFXI

**G. Bibliography of available safety and efficacy data including peer reviewed medical literature:**

Spitzer, M. and Chernys, A.E. Monsel's solution-induced artifact in the uterine cervix. *Am J Obstet Gynecol*, 1996; 175(5): 1204-1207.

Su, G. B. Clinical experience on efficacy of Monsel's solution. *Chung Hua Wai Ko Tsa Chih*, 1981; 19(11): 685-686.

Monsel's Solution. *Pharmaceuticals*. (NY: Wiley, 1987) 1007-1008.



**H. Information about dosage forms used:**

Solution

**I. Information about strength:**

20-22mg per 100ml  
Undiluted

**J. Information about route of administration:**

Topically

**K. Stability data:**

**L. Formulations:**

Oxidizing ferrous sulfate with nitric acid  
See file for compounding directions

**M. Miscellaneous Information:**

CERTIFICATE OF ANALYSIS

30-1168  
# 54812

DUCT: FERRIC SUBSULFATE SOLUTION (PURIFIED)  
RELEASE #: 104273 LOT # :B62908M10

GRADE: --  
CODE:G09-21250/97

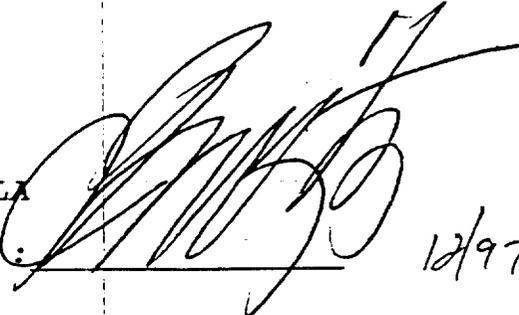
|                           | SPECIFICATIONS       | RESULT      |
|---------------------------|----------------------|-------------|
| 1. DESCRIPTION            | REDDISH-BROWN LIQUID | CONFORMS    |
| 2. Identification         | To pass test         | Passes test |
| 3. Assay (Fe) [gm/100 ml] | 20 - 22%             | 21.2%       |
| 4. Nitrate                | Negative             | Negative    |
| 5. Ferrous salts          | Negative             | Negative    |
| 6. Solubility             | To pass test         | Passes test |

ATTENTION: TONY HATCHETT

Date :11/13/97

Prepared by : A. KASHWALA

10907

Approved by : 

12/97

Our Order # 239573-1 Your PO # 54504

THE ABOVE TEST RESULTS HAVE BEEN OBTAINED BY OUR MANUFACTURER/SUPPLIER AND/OR IN OUR QUALITY CONTROL LABORATORY. THE DATA IS PROVIDED AT THE REQUEST OF AND FOR THE CONVENIENCE OF THE CUSTOMER AND DOES NOT RELIEVE THE CUSTOMER OF ITS RESPONSIBILITY TO VERIFY IT. THIS ANALYSIS IS NOT TO BE CONSTRUED AS A WARRANTY, EXPRESSED OR IMPLIED.

QUALITY CONTROL REPORT

CHEMICAL NAME.: <sup>A</sup>(FERRIC SUBSULFATE) <sup>666</sup>(MONSEL'S SOLN)

MANUFACTURE LOT NO.: C63940C26

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP \_\_\_/BP \_\_\_/MERCK \_\_\_/NF \_\_\_/MART. \_\_\_/CO. SPECS. \_\_\_.

1) DESCRIPTION.:

(REDDISH-BROWN LIQUID; ALMOST ODORLESS; SOUR, STRONGLY ASTRINGENT TASTE; AFFECTED BY LIGHT.

2) SOLUBILITY.:

MISCIBLE WITH WATER AND IN ALCOHOL; ACID TO LITMUS.

3) MELTING POINT.:

4) SPECIFIC GRAVITY.: 1.548.

5) IDENTIFICATION.:

- A) FERROUS SALTS TEST GIVES NEGATIVE RESULTS.
- B) FERRIC SALTS TEST GIVES POSITIVE RESULTS.

PASSES.: \_\_\_\_\_

FAILS.: \_\_\_\_\_

COMMENTS.: NOTE - MAY CRYSTALLIZE OR SOLIDIFY AT LOW TEMPERATURES. K

ANALYST SIGNATURE.: \_\_\_\_\_

DATE.: \_\_\_\_\_

PREPACK TEST.: \_\_\_\_\_

DATE.: \_\_\_\_\_

INITIAL.: \_\_\_\_\_

RETEST.: \_\_\_\_\_

DATE.: \_\_\_\_\_

INITIAL.: \_\_\_\_\_

MALLINCKRODT BAKER -- FERRIC SUBSULFATE SOLUTION - FERRIC SUBSULFATE SOLUTION  
MATERIAL SAFETY DATA SHEET  
NSN: 6505012078245  
Manufacturer's CAGE: 70829  
Part No. Indicator: A  
Part Number/Trade Name: FERRIC SUBSULFATE SOLUTION

=====  
General Information  
=====

Item Name: FERRIC SUBSULFATE SOLUTION  
Company's Name: MALLINCKRODT BAKER INC.  
Company's Street: 222 RED SCHOOL LANE  
Company's City: PHILLIPSBURG  
Company's State: NJ  
Company's Country: US  
Company's Zip Code: 08865-2219  
Company's Emerg Ph #: 908-859-2151/800-424-9300 (CHEMTREC)  
Company's Info Ph #: 201-859-2151  
Record No. For Safety Entry: 001  
Tot Safety Entries This Stk#: 001  
Status: SE  
Date MSDS Prepared: 22AUG95  
Safety Data Review Date: 30OCT96  
Supply Item Manager: KX  
MSDS Preparer's Name: UNKNOWN  
MSDS Serial Number: BNVDB  
Specification Number: NONE  
Spec Type, Grade, Class: NOT APPLICABLE  
Hazard Characteristic Code: J6  
Unit Of Issue: BT  
Unit Of Issue Container Qty: 500 ML  
Type Of Container: STD COML PKG  
Net Unit Weight: 3.2 LBS

=====  
Ingredients/Identity Information  
=====

Proprietary: NO  
Ingredient: FERRIC SUBSULFATE  
Ingredient Sequence Number: 01  
Percent: 40-45  
NIOSH (RTECS) Number: 1004946FS  
CAS Number: 1310-45-8  
OSHA PEL: NOT ESTABLISHED  
ACGIH TLV: NOT ESTABLISHED  
Other Recommended Limit: NONE RECOMMENDED

-----  
Proprietary: NO  
Ingredient: SULFURIC ACID (SARA III)  
Ingredient Sequence Number: 02  
Percent:

Solution with potassium or sodium hydrate T.S. precipitate, without evolving vapor of ammonia.

The Solution, diluted with 4 volumes of water, being mixed with an excess of potassium or sodium hydrate, and slightly acidulated with acetic acid, a portion of this mixture, and for some time, should not give a white, crystalline precipitate.

A portion of the acidulated and cooled filtrate a little diluted with water, and the liquid heated to boiling, it should give a crystalline precipitate.

1000. *Ferri et Ammonii Citras.*

**FERRI ET AMMONII ACETATIS.**  
**SOLUTION OF IRON AND AMMONIUM ACETATE.**  
**TINCTURA AMMONII ACETATIS, PHARM. 1880. [BASIC MIXTURE.]**

Barium Chloride, twenty cubic centimeters  
 Diluted Acetic Acid, thirty cubic centimeters  
 Ammonium Acetate, two hundred cubic centimeters  
 Distilled Water, one hundred cubic centimeters  
 To make one thousand cubic centimeters

of Ammonium Acetate (which should not be dried), the Diluted Acetic Acid, the Tincture of Ferric Chloride, the Glycerin, and, lastly, the product measure one thousand (1000) cubic centimeters.

should be freshly made, when wanted.

**LIQUOR FERRI NITRATIS.**  
**SOLUTION OF FERRIC NITRATE.**

Solution of Ferric Nitrate [Fe<sub>2</sub>(NO<sub>3</sub>)<sub>6</sub> = 483.1] 10 per cent. of the anhydrous salt, and corresponding amount of metallic iron.

Solution of Ferric Sulphate, one hundred and eighty grammes ..... 180 Gm.  
 Ammonia Water, one hundred and sixty cubic centimeters ..... 160 Cc.  
 Nitric Acid, seventy-one grammes ..... 71 Gm.  
 Distilled Water,  
 Water, each, a sufficient quantity,

To make one thousand grammes.... 1000 Gm.

Mix the Ammonia Water with five hundred (500) cubic centimeters of cold Water, and the Solution of Ferric Sulphate with fifteen hundred (1500) cubic centimeters of cold Water. Add the latter solution slowly to the diluted Ammonia Water, with constant stirring. Let the mixture stand until the precipitate has subsided as far as practicable, and then decant the supernatant liquid. Add to the precipitate one thousand (1000) cubic centimeters of cold Water, mix well, and again set the mixture aside, as before. Repeat the washing with successive portions of cold Water, in the same manner, until the washings produce but a slight cloudiness with barium chloride test-solution. Pour the washed ferric hydrate on a wet muslin strainer, and let it drain thoroughly. Then transfer it to a porcelain capsule, add the Nitric Acid, and stir with a glass rod, until a clear solution is obtained. Finally, add enough Distilled Water to make the finished product weigh one thousand (1000) grammes. Filter, if necessary.

A clear, amber-colored or reddish liquid, odorless, having an acid, styptic taste, and an acid reaction.

Specific gravity: about 1.050 at 15° C. (59° F.).

The Solution gives a brownish-red precipitate with ammonia water, and a blue one with potassium ferrocyanide T.S.

If a clear crystal of ferrous sulphate be added to a cooled mixture of equal parts of the Solution and of concentrated sulphuric acid, the crystal will become brown and be surrounded by a brownish-black zone.

If 1.12 (1.1176) Gm. of the Solution be introduced into a glass-stoppered bottle (having a capacity of about 100 Cc.), together with 15 Cc. of water and 1 Cc. of hydrochloric acid, and, after the addition of 1 Gm. of potassium iodide, the mixture be kept for half an hour at a temperature of 40° C. (104° F.), then cooled, and mixed with a few drops of starch T.S., it should require about 2.8 Cc. of decinormal sodium hyposulphite V.S. to discharge the blue-greenish color of the liquid (each Cc. of the volumetric solution indicating 10 per cent. of metallic iron).

**LIQUOR FERRI SUBSULPHATIS.**

**SOLUTION OF FERRIC SUBSULPHATE.**

(SOLUTION OF BASIC FERRIC SULPHATE. MONSEL'S SOLUTION.)

Aqueous solution of Basic Ferric Sulphate (of variable chemical composition), corresponding to about 13.6 per cent. of metallic iron.

Ferrous Sulphate, in clear crystals, *six hundred and  
 seventy-five grammes* ..... 675  
 Sulphuric Acid, *sixty-five grammes* ..... 65  
 Nitric Acid,  
 Distilled Water, each, *a sufficient quantity*,  
 To make *one thousand grammes* . . . . . 1000

Add the Sulphuric Acid to *five hundred (500) cubic centimetres* of  
 Distilled Water in a capacious porcelain capsule, heat the mixture  
 to nearly 100° C. (212° F.), then add *sixty-five (65) grammes* of  
 Acid, and mix well. Divide the Ferrous Sulphate, coarsely powdered,  
 into four equal portions, and add these portions, one at a time, to  
 the hot liquid, stirring after each addition until effervescence ceases.  
 When all of the Ferrous Sulphate is dissolved, add a few drops of  
 Nitric Acid, and, if this causes a further evolution of red fumes, con-  
 tinue to add Nitric Acid, a few drops at a time, until it no longer  
 causes red fumes to be evolved; then boil the Solution until it acquires  
 a ruby-red color and is free from nitrous odor. Lastly, add  
 Distilled Water to make the product weigh *one thousand (1000) grammes*.  
 Keep the product in well-stoppered bottles, in a moderate temperature  
 place (not under 22° C. or 71.6° F.), protected from light.

This solution will sometimes crystallize, forming a semi-solid  
 mass. When this occurs, the application of a gentle heat to the  
 mass will restore the liquid condition.

NOTE.—Solution of Ferric Subsulphate is to be dispensed as such.  
 Solution of Persulphate of Iron has been prescribed by the Pharmacopoeia.

A dark reddish-brown liquid, odorless or nearly so, of an astringent  
 styptic taste, and an acid reaction.

Specific gravity: about 1.550 at 15° C. (59° F.).

Miscible with water and alcohol, in all proportions, without decomposition.

The diluted Solution yields a brownish-red precipitate with ammonium  
 a blue one with potassium ferrocyanide T.S., and a white one with  
 hydrochloric acid, with barium chloride T.S.

On slowly mixing 2 volumes of the Solution with 1 volume of  
 sulphuric acid, in a beaker, a semi-solid, white mass will separate  
 (difference from *tersulphate*).

On adding a clear crystal of ferrous sulphate to a cooled mixture of  
 volumes of concentrated sulphuric acid and a diluted portion of  
 the crystal should not become brown, nor should there be a brown  
 color developed around it (absence of *nitric acid*).

If to a small portion of the Solution, diluted with about 10  
 water, a few drops of freshly prepared potassium ferricyanide T.S.  
 a pure brown color should be produced, without a tinge of green  
 blue (absence of *ferrous salt*).

If 1.12 (1.1176) Gm. of the Solution be introduced into a glass  
 bottle (having a capacity of about 100 Cc.), together with 15 Cc.  
 2 Cc. of hydrochloric acid, and, after the addition of 1 Gm. of  
 iodide, the mixture be kept for half an hour at a temperature of

with physiological salt solution and slowly administered intravenously.

**Dosage Forms**—Injection USP: 50 mg/5 ml, 250 mg/25 ml; for Injection USP: 50 mg.

#### Other Anticoagulant Antagonists

**Tolonium Chloride** [Toluidine Blue; Blutene (*Abbott*)] is 3-amino-7-(dimethylamino)-2-methylphenazathionium chloride [C<sub>15</sub>H<sub>16</sub>ClN<sub>3</sub>S]. **Description and Solubility:** A dark-green powder. 1 Gm dissolves in about 26 ml of water,

yielding a blue to violet solution, and in about 175 ml of alcohol, yielding a blue solution. **Uses:** It precipitates heparin. It is used for the treatment of overdosage of heparin and for the treatment of certain hemorrhagic states, some of which, but not all, are associated with elevated blood heparinoid levels. The organs are stained blue and the urine becomes pale blue-green. Nausea, vomiting, burning sensation upon urination, and tenesmus may occur, but they may be avoided by adequate fluid intake. **Dose:** Oral, 200 to 300 mg daily for menorrhagia; intramuscular or slow intravenous, for heparin overdosage, 100 mg. **Veterinary Dose:** Oral, Dogs and Cats, 200 to 300 mg daily.

#### Hemostatics and Styptics

Many substances not especially related to the clotting mechanism are capable of promoting clotting. Upon contact with most surfaces, platelets disintegrate, thereby liberating a thromboplastin. Spongy and gauzy materials, which provide a large surface area, are thus used to arrest bleeding; absorbable sponges may be left permanently at the site of bleeding. Fibrin, fibrinogen, and thrombin are also potent hemostatics (see page 829). Astringents (see Chapter 43, page 768) also initiate clotting by precipitating proteins and by labilizing platelets; ferric salts are mostly employed as styptics.

**Alum**—see page 769.

**Cellulose, Oxidized**—see page 1876.

**Estrogens, Conjugated**—see page 991.

**Ferric Chloride**—see page 772.

**Fibrinogen**—see page 830.

**Fibrinogen with Antihemophilic Factor**—see page 830.

#### Absorbable Gelatin Sponge USP

[Gelfoam (*Upjohn*)]

Absorbable Gelatin Sponge is gelatin in the form of a sterile, absorbable, water-insoluble sponge.

**Description**—A light, nearly white, nonelastic, tough, porous, hydrophilic solid. A 10-mm cube weighing approximately 9 mg will take up approximately 45 times its weight of well-agitated oxalated whole blood. It is stable in dry heat at 150° for 4 hours.

**Solubility**—Insoluble in water, but absorbable in body fluids; completely digested by a solution of pepsin.

**Uses**—Absorbable Gelatin Sponge is a hemostatic and coagulant used to control bleeding. It is moistened with thrombin solution or sterile normal saline and may then be left in place following the closure of a surgical incision. It is absorbed in from 4 to 6 weeks.

**Human Antihemophilic Factor**—see page 830.

**Antihemophilic Human Plasma**—see page 830.

**Protamine Sulfate**—see page 836.

**Thrombin**—see page 831.

**Thromboplastin**—see page 1376.

**Tolonium Chloride**—see this page.

#### Other Hemostatics and Styptics

**Carbazochrome Salicylate** [Adrenosem (*Massengill*); Adrestat (*Organon*)]—An adrenochrome monosemicarbazone [3-hydroxy-1-methyl-5,6-indolinedione-5-semicarbazone] sodium salicylate complex [C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>·C<sub>7</sub>H<sub>5</sub>NaO<sub>3</sub>] occurring as a fine, orange-red, odorless powder with a sweetish saline taste. It is soluble in both alcohol and water. A 13% aqueous solution has a pH range of 6.7–7.3. **Uses:** Proposed for the systemic control of capillary bleeding of various types. Its clinical usefulness for this purpose is scientifically unjustified. **Dose:** Oral, 1 to 5 mg 4 times daily; intramuscular, 5 mg every 2 to 4 hours.

**Ferric Subsulfate** [approx. Fe<sub>2</sub>O(SO<sub>4</sub>)<sub>3</sub>·H<sub>2</sub>O]—Used and prepared only as a solution. Ferric Subsulfate Solution was official in NF XI. It is prepared by oxidizing ferrous sulfate with nitric acid. The solution contains 20–22 Gm Fe per 100 ml. It is reddish brown and has an astringent, sour taste. It is miscible with alcohol. **Uses:** An important styptic solution. The solution is less irritating than ferric sulfate because of the lesser amount of sulfuric acid present. It is occasionally used to control surface bleeding and as an astringent in a variety of skin disorders. It should not be used in vesicular, bulbous, or exudative dermatoses, because it may then cause permanent pigmentation of the skin.

**Fibrin Foam Human**—A dry artificial sponge of human fibrin, prepared by clotting with thrombin a foam of a solution of human fibrinogen. The clotted foam is dried from the frozen state and heated at 130° for 3 hours to sterilize. It appears as a fine, white sponge of firm texture. It is insoluble in water. **Uses:** A mechanical coagulant of blood in case of hemorrhage, especially in surgery of the brain, liver, kidneys, and other organs where ordinary methods of hemostasis are ineffective or inadvisable. This preparation is used by impregnating it with a freshly prepared solution of thrombin in normal saline solution and then applying the foam to the bleeding area. In time, the foam is absorbed.

#### Electrolytes

The concentration of several of the electrolytes in the plasma is critical for the proper functioning of the cells, especially those of the excitable tissues. For the normal plasma concentration of the principal electrolytes, see page 815. The proper balance of the several ions is complex; it depends not alone upon the concentration

in the extracellular fluid (of which plasma is one compartment) but also upon the intracellular concentration, the ratio across the cell membrane being an essential factor, and upon the ratio of one ion type to another. Thus, the plasma electrolyte concentrations provide only a crude clue to the electrolyte status of the patient.

Ferric chloride has been exposed to daylight for some time yields a greenish or bluish color which is due to ferricyanide T.S. (presence of ferrous salt).

**Nitrate**—Dilute 4 ml. of Ferric Chloride Tincture with 10 ml. of water, heat the solution to boiling and pour it into a mixture of 10 ml. of water and 10 ml. of ammonia T.S. Filter the mixture while hot, and wash the filter with water until the total filtrate measures 30 ml. Mix the filtrate well and to 5 ml. add 2 drops of indigo carmine T.S. Mix this solution with 1 ml. of sulfuric acid: the blue color does not appear within 1 minute.

**Assay**—Transfer 5 ml. of Ferric Chloride Tincture, accurately measured, to a flask of suitable capacity. Add about 20 ml. of water, 3 Gm. of potassium iodide, and 3 ml. of hydrochloric acid. Allow the solution to stand during 15 minutes; dilute it with 100 ml. of water, and then titrate with 0.1 N sodium thiosulfate, using starch T.S. as the indicator. Each ml. of 0.1 N sodium thiosulfate is equivalent to 16.22 mg. of  $\text{FeCl}_3$ .

**Alcohol content**, page 404—Ferric Chloride Tincture contains from 58 to 64 per cent of  $\text{C}_2\text{H}_5\text{OH}$ .

**Packaging and storage**—Preserve Ferric Chloride Tincture in tight, light-resistant containers and avoid exposure to direct sunlight or to excessive heat.

**CATEGORY**—Astringent; hematinic.  
**USUAL DOSE**—0.6 ml.

### Ferric Citrochloride Tincture

Ferric Citrochloride Tincture is a hydroalcoholic solution containing, in each 100 ml., ferric citrochloride equivalent to not less than 4.48 Gm. of Fe.

|                               |          |
|-------------------------------|----------|
| Ferric Chloride Solution..... | 350 ml.  |
| Sodium Citrate.....           | 450 Gm.  |
| Alcohol.....                  | 150 ml.  |
| Water, a sufficient quantity, |          |
| To make about.....            | 1000 ml. |

Mix the ferric chloride solution with 150 ml. of water, dissolve the sodium citrate in the mixture with the aid of gentle heat, and add the alcohol. When the solution has become cold, add sufficient water to make the product measure 1000 ml. Set the Ferric Citrochloride Tincture aside in a cold place for a few days so that the excess of saline matter may separate, and then filter.

**Assay**—Transfer 5 ml. of Ferric Citrochloride Tincture, accurately measured, into an iodine flask, add 7 ml. of hydrochloric acid and 25 ml. of water, and heat on a water bath until clear. Cool to room temperature and add about 25 ml. of water and 3 Gm. of potassium iodide, and allow the mixture to stand for 15 minutes. Then remove the stopper and the sides of the flask with

additional 50 ml. of water and titrate the liberated iodine with 0.1 N sodium thiosulfate, using starch T.S. as the indicator. Each ml. of 0.1 N sodium thiosulfate is equivalent to 5.585 mg. of Fe.

**Alcohol content**, page 404—Ferric Citrochloride Tincture contains from 13 to 15 per cent of  $\text{C}_2\text{H}_5\text{OH}$ .

**Packaging and storage**—Preserve Ferric Citrochloride Tincture in tight, light-resistant containers and avoid exposure to direct sunlight or to excessive heat.

**CATEGORY**—Hematinic.  
**USUAL DOSE**—0.5 ml.  
One usual dose represents about 22 mg. of iron in the form of ferric citrochloride.

### SOLUBLE FERRIC PHOSPHATE

Ferric Phosphate with Sodium Citrate

Soluble Ferric Phosphate is ferric phosphate rendered soluble by the presence of sodium citrate, and yields not less than 12 per cent and not more than 15 per cent of Fe.

**Description**—Soluble Ferric Phosphate occurs as thin, bright green, transparent scales, or as granules. It is without odor, and has an acid, slightly salty taste. Soluble Ferric Phosphate is stable in dry air when protected from light, but when unprotected, soon becomes discolored. A solution of Soluble Ferric Phosphate (1 in 10) is acid to litmus.

**Solubility**—Soluble Ferric Phosphate dissolves freely in water. It is insoluble in alcohol.

**Identification**—

**A:** To 10 ml. of a solution of Soluble Ferric Phosphate (1 in 100) add ammonia T.S., dropwise: the solution becomes reddish brown, but no precipitate forms.

**B:** Remove the iron from 10 ml. of a solution of Soluble Ferric Phosphate (1 in 10) by boiling it with an excess of sodium hydroxide T.S.; filter, and strongly acidify the filtrate with hydrochloric acid: a cooled portion of this liquid mixed with an equal volume of magnesia mixture T.S. and treated with a slight excess of ammonia T.S. produces an abundant, white, crystalline precipitate. This precipitate, after being washed, turns greenish yellow when treated with a few drops of silver nitrate T.S. (distinction from pyrophosphate).

**Ammonium salts**—Boil about 100 mg. of Soluble Ferric Phosphate with 5 ml. of sodium hydroxide T.S.: a reddish brown precipitate forms without the evolution of ammonia.

**Lead**—Dissolve 1 Gm. of Soluble Ferric Phosphate in 3 ml. of nitric acid (1 in 2) in a 100-ml. volumetric flask. Add sufficient water to make 100 ml., and mix well. A 10-ml. portion of this solution contains no more than 5 mcg. of lead (corresponding to not more than 50 parts per million) when treated according to the *Lead Limit Test*, page 414, using 10 ml. of ammonium citrate solution, 3 ml. of potassium cyanide solu-

tion, and 1 ml. of hydroxylamine hydrochloride solution.

**Assay**—Dissolve about 1 Gm. of Soluble Ferric Phosphate, accurately weighed, in 25 ml. of water and 5 ml. of hydrochloric acid in a glass-stoppered flask; add 4 Gm. of potassium iodide, securely stopper the flask, and allow the mixture to stand 15 minutes; dilute with 50 ml. of water, and titrate the liberated iodine with 0.1 N sodium thiosulfate, using starch T.S. as the indicator. Perform a blank determination with the same quantities of the same reagents and in the same manner and make any necessary correction. Each ml. of 0.1 N sodium thiosulfate is equivalent to 5.585 mg. of Fe.

**Packaging and storage**—Preserve Soluble Ferric Phosphate in well-closed, light-resistant containers.

**CATEGORY**—Hematinic.  
**USUAL DOSE**—250 mg.

### FERRIC SUBSULFATE SOLUTION

Monsel's Solution; Basic Ferric Sulfate Solution

Ferric Subsulfate Solution is a water solution containing, in each 100 ml., basic ferric sulfate equivalent to not less than 20 Gm. and not more than 22 Gm. of Fe.

**NOTE:** If exposed to low temperatures, crystallization may take place in the Solution. The crystals will redissolve upon warming the Solution.

**Description**—Ferric Subsulfate Solution is a reddish brown liquid, odorless or nearly so, with a sour, strongly astringent taste. Ferric Subsulfate Solution is acid to litmus, and it is affected by light. Its specific gravity is about 1.548.

**Solubility**—Ferric Subsulfate Solution is miscible with water and with alcohol.

**Identification**—Separate portions of a dilution of Ferric Subsulfate Solution (1 in 20) yield a brownish red precipitate with ammonia T.S., a blue precipitate with potassium ferrocyanide T.S., and a white precipitate, insoluble in hydrochloric acid, with barium chloride T.S.

**Nitrate**—Add a clear crystal of ferrous sulfate to a cooled mixture of equal volumes of sulfuric acid and a dilution of Ferric Subsulfate Solution (1 in 10): the crystal does not become brown, nor does a brownish black color develop around it.

**Ferrous salts**—Add a few drops of freshly prepared potassium ferricyanide T.S. to 2 ml. of a dilution of Ferric Subsulfate Solution (1 in 20): a brown color is produced and the solution remains free from even a transient green or greenish blue color.

**Assay**—Dilute about 10 ml. of Ferric Subsulfate Solution, accurately measured, to exactly 100 ml. with water. Transfer 10 ml. of the dilution to a stoppered flask; add 5 ml. of hydrochloric acid and 3 Gm. of potassium iodide.

Stopper the flask, and allow the mixture to stand for 15 minutes; then dilute with 50 ml. of water, and titrate the liberated iodine with 0.1 N sodium thiosulfate, using starch T.S. as the indicator. Each ml. of 0.1 N sodium thiosulfate is equivalent to 5.585 mg. of Fe.

**Packaging and storage**—Preserve Ferric Sub-sulfate Solution in tight, light-resistant containers, and in a moderately warm place (not under 22°).

**CATEGORY**—Astringent.

**AS A STYPTIC**—Use Ferric Sub-sulfate Solution undiluted.

### FERROUS CARBONATE PILLS

Chalybeate Pills  
Blaud's Pills  
Ferruginous Pills

Each Pill contains not less than 60 mg. of  $\text{FeCO}_3$ .

|  |     |     |
|--|-----|-----|
| Ferrous Sulfate, in clear crystals....       | 16  | Gm. |
| Potassium Carbonate.....                     | 9.5 | Gm. |
| Sucrose, finely powdered.....                | 4   | Gm. |
| Tragacanth, finely powdered.....             | 1   | Gm. |
| Althea, in very fine powder.....             | 1   | Gm. |
| Glycerin,                                    |     |     |
| Purified Water, each, a sufficient quantity, |     |     |

To make 100 pills.

Triturate the potassium carbonate in a mortar with a sufficient quantity (about 5 drops) of glycerin, add the ferrous sulfate and sucrose, previously triturated together to a uniform, fine powder, and mix the mass thoroughly until it assumes a greenish color. When the reaction is complete, incorporate the tragacanth and althea, and add purified water, if necessary, to obtain a mass of pilular consistency. Divide it into 100 pills.

**Assay**—Carefully pulverize 5 Ferrous Carbonate Pills in a mortar, and triturate with 20 ml. of diluted sulfuric acid until all carbonate is dissolved. Transfer completely the contents of the mortar to a beaker of about 800-ml. capacity, and add water to bring the total volume to approximately 300 ml. Add orthophenanthroline T.S., and titrate immediately with 0.1 N ceric sulfate, avoiding excessive stirring. Near the end of the titration tilt the beaker at an angle of 45° to facilitate the detection of the end point. Each ml. of 0.1 N ceric sulfate is equivalent to 11.59 mg. of  $\text{FeCO}_3$ .

**Packaging and storage**—Preserve Ferrous Carbonate Pills in well-closed containers.

**CATEGORY**—Hematinic.

**USUAL DOSE**—5 pills.

### FERROUS IODIDE SYRUP

Ferrous Iodide Syrup contains, in each ml., not less than 6.5 Gm. and not more than 7.5 Gm. of  $\text{FeI}_2$ , representing approximately per cent of  $\text{FeI}_2$ , by weight.

Ferrous Iodide Syrup may be prepared follows:

|   |      |   |
|---|------|---|
| Iron, in the form of fine, bright wire..... | 20   | G |
| Iodine.....                                 | 60   | G |
| Hypophosphorous Acid.....                   | 5    | m |
| Sucrose.....                                | 850  | G |
| Purified Water, a sufficient quantity,      |      |   |
| To make.....                                | 1000 | m |

**NOTE:** For the purpose of retarding coloration, 1.3 Gm. of citric acid may replace the hypophosphorous acid in the above formula.

Place the iron in a flask having a capacity about 500 ml., add the iodine and 200 ml. purified water, and shake the mixture occasionally, checking the reaction, if necessary, placing the flask in cold water. When the liquid has acquired a green color and has lost the odor of iodine, heat it to boiling, and dissolve 100 Gm. of sucrose in the hot liquid. Filter the solution at once into a flask graduated to 1000 ml. and containing the remainder of the sucrose, and rinse the flask containing the iron with 240 ml. of hot purified water, divided portions, passing the rinsings successively through the filter. Agitate the mixture until the sucrose is dissolved, warming if necessary, cool to 25°, and add the hypophosphorous acid and enough purified water to make the product measure 1000 ml. Mix and strain.

**Description**—Ferrous Iodide Syrup is a transparent, pale, yellowish green, syrupy liquid having a sweet, ferruginous taste and a slight acid reaction. Its specific gravity is about 1.05.

**Identification**—

**A:** Add a few drops of potassium ferrocyanide T.S. to 5 ml. of Ferrous Iodide Syrup; blue precipitate forms.

**B:** Mix 5 ml. of Ferrous Iodide Syrup with a few drops of starch T.S., and add 3 drops of chlorine T.S.; the liquid acquires a deep blue color.

**Free iodine**—To about 5 ml. of Ferrous Iodide Syrup add a few drops of starch T.S.; no blue color is produced.

**Assay**—Place exactly 10 ml. of Ferrous Iodide Syrup in a flask, dilute it with 30 ml. of water, add 50.0 ml. of 0.1 N silver nitrate, and 5 ml. of nitric acid, and heat on a water bath until a precipitate of silver iodide is greenish yellow. Cool, add 2 ml. of ferric ammonium sulfate T.S. and determine the residual silver nitrate by titration.





**TITLE:** Monsel's solution-induced artifact in the uterine cervix.

**AUTHOR:** Spitzer M; Chernys AE

**AUTHOR AFFILIATION:** Department of Obstetrics and Gynecology, Queens Hospital Center, Jamaica, NY 11432, USA.

**SOURCE:** Am J Obstet Gynecol 1996 Nov;175(5):1204-7

**NLM CIT. ID:** 97097948

**ABSTRACT:** We documented and quantified Monsel's solution-related artifacts after cervical biopsies. All loop electro-surgical cone biopsy specimens over a 3-month period were reviewed for necrosis artifact of the surface epithelium. The degree of change was quantified and correlated with the antecedent use of Monsel's solution. Twenty-four cone biopsy specimens were evaluated. Three of the eight cone biopsy specimens obtained fewer than 10 days after the use of Monsel's solution showed definite changes. Between 10 and 18 days after the use of Monsel's solution, four of eight specimens showed change. After 18 days, none of eight specimens showed change. One specimen at 18 days showed focal changes that seemed to be related to the use of an unusually large amount of Monsel's solution, because the patient had had six biopsies within 2 days. The routine use of Monsel's solution may interfere with the ability to recognize and characterize disease process in cone biopsy specimens when the cone procedure is done within 3 weeks after the use of Monsel's solution.

G

**MAIN MESH SUBJECTS:** Cervix Uteri/DRUG EFFECTS/\*PATHOLOGY  
 Ferric Compounds/\*ADVERSE EFFECTS  
 Sulfates/\*ADVERSE EFFECTS

**ADDITIONAL MESH SUBJECTS:** Artifacts  
 Biopsy  
 Female  
 Human

**PUBLICATION TYPES:** JOURNAL ARTICLE

**LANGUAGE:** Eng

**REGISTRY NUMBERS:** 0 (Ferric Compounds)  
 0 (Sulfates)  
 1310-45-8 (ferric subsulfate solution)



Order Documents

52,71 Other Years

Log off IGM

Next Record

Details of Search

Return to Results

Return to Search Screen

Previous Record

### National Library of Medicine: IGM Full Record Screen



|                         |                        |                   |
|-------------------------|------------------------|-------------------|
| Order Documents         | 92, 67, 71 Other Years | Log off IGM       |
| Next Record             | Details Of Search      | Return to Results |
| Return to Search Screen | Previous Record        |                   |



**TITLE:** Stopping cervical bleeding.

**AUTHOR:** Manca DP

**SOURCE:** Can Fam Physician 1997 Dec;43:2121

**NLM CIT. ID:** 98088367

**MAIN MESH SUBJECTS:** \*Cervix Uteri/INJURIES \*  
 Ferric Compounds/\*ADMINISTRATION & DOSAGE  
 Hemorrhage/ETIOLOGY/\*THERAPY  
 Hemostatics/\*ADMINISTRATION & DOSAGE  
 Sulfates/\*ADMINISTRATION & DOSAGE

**ADDITIONAL MESH SUBJECTS:** Biopsy/ADVERSE EFFECTS  
 Female  
 Human  
 Time Factors

**PUBLICATION TYPES:** JOURNAL ARTICLE

**LANGUAGE:** Eng

**REGISTRY NUMBERS:** 0 (Ferric Compounds)  
 0 (Hemostatics)  
 0 (Sulfates)  
 1310-45-8 (ferric subsulfate solution)



|                         |                        |                   |
|-------------------------|------------------------|-------------------|
| Order Documents         | 92, 67, 71 Other Years | Log off IGM       |
| Next Record             | Details Of Search      | Return to Results |
| Return to Search Screen | Previous Record        |                   |

### National Library of Medicine: IGM Full Record Screen



Order Documents

52, 67, 71 Other Years

Log off IGM

Next Record

Details Of Search

Return to Results

Return to Search Screen

Previous Record



**TITLE:**



[Clinical experience on efficacy of Monsel's solution (author's transl)]



**AUTHOR:**

Su GB

**SOURCE:**

Chung Hua Wai Ko Tsa Chih 1981 Nov;19(11):685-6

**NLM CIT. ID:**

82185983

**MAIN MESH SUBJECTS:**

Ferric Compounds/\*THERAPEUTIC USE  
Hemorrhage/\*DRUG THERAPY  
Hemostatics/\*THERAPEUTIC USE  
Iron/\*THERAPEUTIC USE  
Sulfates/\*THERAPEUTIC USE

**ADDITIONAL MESH SUBJECTS:**

Adult  
Aged  
Case Report  
English Abstract  
Human  
Male

**PUBLICATION TYPES:**

JOURNAL ARTICLE

**LANGUAGE:**

Chi

**REGISTRY NUMBERS:**

0 (Ferric Compounds)  
0 (Hemostatics)  
0 (Sulfates)  
1310-45-8 (ferric subsulfate solution)  
7439-89-6 (Iron)

### National Library of Medicine: IGM Full Record Screen



Order Documents

32 71 Other Years

Log off IGM

Next Record

Details Of Search

Return to Results

Return to Search Screen

Previous Record



**TITLE:** Practice tips. Mole no more.  
**AUTHOR:** Manca DP  
**SOURCE:** Can Fam Physician 1997 Aug;43:1359  
**NLM CIT. ID:** 97411097  
**MAIN MESH SUBJECTS:** Ferric Compounds/\***THERAPEUTIC USE**  
 Hemostatics/\***THERAPEUTIC USE**  
 Nevus/\*SURGERY  
 Skin Neoplasms/\*SURGERY  
 Sulfates/\***THERAPEUTIC USE**

**ADDITIONAL MESH SUBJECTS:** Human  
Wound Healing

**PUBLICATION TYPES:** JOURNAL ARTICLE

**LANGUAGE:** Eng

**REGISTRY NUMBERS:** 0 (Ferric Compounds)  
 0 (Hemostatics)  
 0 (Sulfates)  
 1310-45-8 (ferric subsulfate solution)



Order Documents

32 71 Other Years

Log off IGM

Next Record

Details Of Search

Return to Results

Return to Search Screen

Previous Record

# Practice Tips

Donna P. Manca, MD, CCFP

## Stopping cervical bleeding

### Indications

This technique can be used for controlling cervical bleeding from a biopsied site. Occasionally, women present to me with bleeding after cervical biopsy or laser treatment for abnormal Pap smears. When they do present, bleeding is usually minimal and settles with watchful waiting. Occasionally a low-grade infection requires antibiotic treatment. On two occasions in my practice, bleeding was excessive and persistent after cervical biopsy or laser or loop excision. Examination of the cervix revealed an oozing injured site. I was able to stop the bleeding by applying Monsel's solution (20% ferric subsulfate) to the cervix.

This method is contraindicated when bleeding is from inside the os cervix or when excessive hemorrhaging requires further intervention.

### Procedure

With ringed forceps and gauze, dab the cervix to identify the site of bleeding. Then, using ringed forceps with 2×2 gauze soaked in Monsel's solution, apply the solution directly to the bleeding site.

### Discussion

The women I treated were discharged with no further complications or complaints.

Upon reviewing the literature, I found that Monsel's solution is often used in gynecologic oncology for bleeding from cervical and vaginal biopsies. One report<sup>1</sup> described a brownish vaginal discharge that appeared several days after the application of Monsel's when a vaginal pack soaked in Monsel's had been used. Monsel's solution is recommended over sutures after cold-knife conization in studies comparing these two methods of hemostasis.<sup>2,3</sup> Monsel's solution also has been used in examining the vagina for papilloma virus and neoplasia.<sup>4</sup>

I could find no information in the literature on adverse effects for future Pap smears. Necrosis artifact could appear if cervical biopsy is performed within 3 weeks after application of Monsel's solution.<sup>1</sup> Monsel's solution appears to be a safe method for controlling cervical bleeding in this situation. Be aware that biopsies done within 3 weeks of using Monsel's solution can show artifacts. ♦

### References

1. Rariff C. Preventing cervical bleeding with Monsel's solution. *Oncol Nurs Forum* 1992;19(4):664.
2. Gilbert L, Saunders NJ, Strünger R, Sharp F. Hemostasis and cold knife cone biopsy: a prospective, randomized trial comparing a suture versus non-suture technique. *Obstet Gynecol* 1989; 74(4):640-3.
3. Tangtrakul S, Srisupundit S, Linasmita V, Bullangpoti S, Israngura N, Wilailak S, et al. A randomized study comparing suture with non-suture cold-knife conization. *J Obstet Gynecol* 1995;21(6):587-91.
4. Davis GD. Colposcopic examination of the vagina. *Obstet Gynecol Clin North Am* 1993;20(1):217-29.
5. Spitzer M, Chernys AE. Monsel's solution-induced artifact in the uterine cervix. *Am J Obstet Gynecol* 1996;175(5):1204-7.

...

We encourage readers to share some of their practice experience: the neat little tricks that solve difficult clinical situations. *Canadian Family Physician* will pay \$50 to authors upon publication of their practice tips.

Dr Manca, a Fellow of the College, practises family medicine in Edmonton.

**A. INGREDIENT NAME:**

**FERRIC SUBSULFATE PURIFIED POWDER**

**B. Chemical Name:**

Approximately  $\text{Fe}_2(\text{SO}_4)_3(\text{OH})_2$

**C. Common Name:**

**D. Chemical grade or description of the strength, quality, and purity of the ingredient:**

Feric Subsulphate (variable)

**E. Information about how the ingredient is supplied:**

Off white to pale yellow to brown fine powder, is odorless.

**F. Information about recognition of the substance in foreign pharmacopeias:**

The Pharmacopeia of the U.S.

**G. Bibliography of available safety and efficacy data including peer reviewed medical literature:**

**H. Information about dosage forms used:**

Topically

**I. Information about strength:**

**J. Information about route of administration:**

Topically

**K. Stability data:**

Decomposition: 520°C

**L. Formulations:**

**M. Miscellaneous Information:**

Please Refer to your P.O.# 54786 for the product listed below.

30-1328

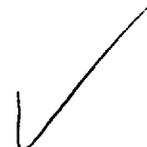
# 54813

CHEMICAL NAME: FERRIC SUBSULFATE PURIFIED

CATALOG NUMBER: F1042

LOT NUMBER: LF0302

Seller certifies that the processes used in the manufacturing of the above items were in compliance with the applicable specifications as referred in or furnished with this purchase order.



Sincerely,

*Lilian D. Casabar*

12/97

LILIAN D. CASABAR  
CofA COORDINATOR

enc /

QUALITY CONTROL REPORT

CHEMICAL NAME.: FERRIC SUBSULFATE POWDER *A*

MANUFACTURE LOT NO.: LF0302

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP \_\_\_/BP \_\_\_/MERCK \_\_\_/NF \_\_\_/MART. \_\_\_/CO. SPECS. \_\_\_.

*E* 1) DESCRIPTION.:

OFF WHITE TO PALE YELLOW TO BROWN FINE POWDER. IS ODORLESS.

2) SOLUBILITY.:

SLIGHTLY SOLUBLE IN WATER AND IN ALCOHOL.

3) MELTING POINT.:

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

A) A SOLUTION RESPONDS TO THE TESTS FOR FERRIC.

PASSES.: \_\_\_\_\_

FAILS.: \_\_\_\_\_

COMMENTS.: PRODUCT GETS AFFECTED BY LIGHT AND AIR.

ANALYST SIGNATURE.: \_\_\_\_\_

DATE.: \_\_\_\_\_

PREPACK TEST.: \_\_\_\_\_

DATE.: \_\_\_\_\_

INITIAL.: \_\_\_\_\_

RETEST.: \_\_\_\_\_

DATE.: \_\_\_\_\_

INITIAL.: \_\_\_\_\_



GARDENA, CA  
NEW BRUNSWICK, NJ

# Material Safety Data Sheet

|                 |      |                               |
|-----------------|------|-------------------------------|
| NFPA            | HMIS | Personal Protective Equipment |
|                 |      |                               |
| See Section 15. |      |                               |

| Section 1. Chemical Product and Company Identification |   | Page Number: 1   |
|--|---|--|
| Common Name/<br>Trade Name                             | Ferric subsulfate   | Code<br>F3150  |
| Manufacturer   | SPECTRUM CHEMICAL MFG. CORP.<br>14422 SOUTH SAN PEDRO STREET<br>GARDENA, CALIFORNIA 90248 | CAS#<br>1310-45-8  |
| Commercial Name(s)                                     | Monsel's Salt   | RTECS<br>Not available.  |
| Synonym  | Basic ferric sulfate  | TSCA<br>On the TSCA list.  |
| Chemical Name  | Not available.  | CI#<br>Not applicable.   |
| Chemical Family  | Salt.   | <b>IN CASE OF EMERGENCY</b><br><b>CHEMTREC (24hr) 800-424-9300</b><br>Emergency phone: (310)516-8000 |
| Chemical Formula                                       | Fe <sub>4</sub> (OH) <sub>2</sub> (SO <sub>4</sub> ) <sub>5</sub>                         |  |
| Supplier   | SPECTRUM QUALITY PRODUCTS, INC.<br>14422 SOUTH SAN PEDRO STREET<br>GARDENA, CA 90248      |  |

| Section 2. Composition and Information on Ingredients |           |   |                           |                           |             |  |
|---|-----------|---|---------------------------|---------------------------|-------------|--|
| Name  | CAS #     | Exposure Limits   |                           |                           | % by Weight |  |
|   |           | TWA (mg/m <sup>3</sup> )  | STEL (mg/m <sup>3</sup> ) | CEIL (mg/m <sup>3</sup> ) |             |  |
| Ferric subsulfate                                     | 1310-45-8 | 1   |                           |                           | 100         |  |
| Toxicological Data on Ingredients                     |           | Ferric subsulfate<br>LD50: Not available.<br>LC50: Not available. |                           |                           |             |  |

| Section 3. Hazards Identification |  |
|-----------------------------------|--|
| Potential Acute Health Effects    | Slightly dangerous to dangerous in case of ingestion. Very slightly to slightly dangerous in case of eye contact (irritant), of inhalation.  |
| Potential Chronic Health Effects  | Very slightly to slightly dangerous in case of eye contact (irritant), of inhalation.<br><b>CARCINOGENIC EFFECTS:</b> Not available. <b>MUTAGENIC EFFECTS:</b> Not available. <b>TERATOGENIC EFFECTS:</b> Not available. The substance is toxic to blood, kidneys, liver. Toxicity of the product to the reproductive system: Not available. Repeated or prolonged exposure to the substance can produce target organs damage.<br><br><b>WARNING:</b> This product contains a chemical known to the State of California to cause cancer.<br>Chemical ingredient(s) requiring this warning:<br><br>NONE<br><br><b>WARNING:</b> This product contains a chemical known to the State of California to cause birth defects or other reproductive harm.<br>Chemical ingredient(s) requiring this warning:<br><br>NONE |

**Section 4. First Aid Measures**

|                             |  |
|-----------------------------|--|
| <b>Eye Contact</b>          | IMMEDIATELY flush eyes with running water for at least 15 minutes, keeping eyelids open. COLD water may be used  |
| <b>Skin Contact</b>         | NO known EFFECT according to our database.   |
| <b>Serious Skin Contact</b> | No additional information.   |
| <b>Inhalation</b>           | Allow the victim to rest in a well ventilated area. Seek immediate medical attention.  |
| <b>Serious Inhalation</b>   | No additional information.   |
| <b>Ingestion</b>            | Remove dentures if any. Have conscious person drink several glasses of water or milk. INDUCE VOMITING by sticking finger in throat. Lower the head so that the vomit will not reenter the mouth and throat. NEVER give an unconscious person anything to ingest. Seek medical attention. |
| <b>Serious Ingestion</b>    | No additional information.   |

**Section 5. Fire and Explosion Data**

|  |   |
|--|---|
| <b>Flammability of the Product</b>                         | Non-flammable.  |
| <b>Auto-Ignition Temperature</b>                           | Not applicable.   |
| <b>Flash Points</b>  | Not applicable.   |
| <b>Flammable Limits</b>                                    | Not applicable.   |
| <b>Products of Combustion</b>                              | Not applicable.   |
| <b>Fire Hazards in Presence of Various Substances</b>      | Not applicable.   |
| <b>Explosion Hazards in Presence of Various Substances</b> | Risks of explosion of the product in presence of mechanical impact: Not available.<br>Risks of explosion of the product in presence of static discharge: Not available.<br>No specific information is available in our database regarding the product's risks of explosion in the presence of various materials |
| <b>Fire Fighting Media and Instructions</b>                | Non-flammable.  |
| <b>Special Remarks on Fire Hazards</b>                     | No additional remark.   |
| <b>Special Remarks on Explosion Hazards</b>                | No additional remark.   |

**Section 6. Accidental Release Measures**

|                    |  |
|--------------------|--|
| <b>Small Spill</b> | Use appropriate tools to put the spilled solid in a convenient waste disposal container. If necessary: Neutralize the residue with a dilute solution of sodium carbonate. Finish cleaning by spreading water on the contaminated surface and dispose of according to local and regional authority requirements   |
| <b>Large Spill</b> | Our database contains no additional information in case of a spill and/or a leak of the product. Use a shovel to put the material into a convenient waste disposal container. Neutralize the residue with a dilute solution of sodium carbonate. Finish cleaning by spreading water on the contaminated surface and allow to evacuate through the sanitary system. |

**Section 7. Handling and Storage**

|                    |   |
|--------------------|---|
| <b>Precautions</b> | No specific safety phrase has been found applicable for this product.   |
| <b>Storage</b>     | No specific storage is required. Use shelves or cabinets sturdy enough to bear the weight of the chemicals. Be sure that it is not necessary to strain to reach materials, and that shelves are not overloaded. |

Continued on Next Page

**Section 8. Exposure Controls/Personal Protection**

|   |   |
|---|---|
| <b>Engineering Controls</b>                         | Use process enclosures, local exhaust ventilation, or other engineering controls to keep airborne levels below recommended exposure limits. If user operations generate dust, fume or mist, use ventilation to keep exposure to airborne contaminants below the exposure limit. |
| <b>Personal Protection</b>                          | Safety glasses. Lab coat.   |
| <b>Personal Protection in Case of a Large Spill</b> | Splash goggles. Full suit. Boots. Gloves. Suggested protective clothing might not be sufficient, consult a specialist BEFORE handling this product.   |
| <b>Exposure Limits</b>                              | TWA: 1 (mg/m <sup>3</sup> ) from OSHA/NIOSH [1993]<br>TWA: 1 (mg/m <sup>3</sup> ) from ACGIH [1993]<br><br>Consult local authorities for acceptable exposure limits.  |

**Section 9. Physical and Chemical Properties**

|                                      |  |              |                |
|--------------------------------------|--|--------------|----------------|
| <b>Physical state and appearance</b> | Solid.                                   | <b>Odor</b>  | Not available. |
| <b>Molecular Weight</b>              | Not available.                           | <b>Taste</b> | Strong.        |
| <b>pH (1% soln/water)</b>            | 4  | <b>Color</b> | Brown.         |
| <b>Boiling Point</b>                 | Not available.                           |              |                |
| <b>Melting Point</b>                 | Decomposes.                              |              |                |
| <b>Critical Temperature</b>          | Not available.                           |              |                |
| <b>Specific Gravity</b>              | Not available.                           |              |                |
| <b>Vapor Pressure</b>                | Not available.                           |              |                |
| <b>Vapor Density</b>                 | Not available.                           |              |                |
| <b>Volatility</b>                    | Not available.                           |              |                |
| <b>Odor Threshold</b>                | Not available.                           |              |                |
| <b>Water/Oil Dist. Coeff.</b>        | Not available.                           |              |                |
| <b>Ionicity (in Water)</b>           | Not available.                           |              |                |
| <b>Dispersion Properties</b>         | See solubility in water.                 |              |                |
| <b>Solubility</b>                    | Easily soluble in cold water, hot water. |              |                |

**Section 10. Stability and Reactivity Data**

|  |  |
|--|--|
| <b>Stability</b>                               | The product is stable.   |
| <b>Instability Temperature</b>                 | Not available.   |
| <b>Conditions of Instability</b>               | No additional remark.  |
| <b>Incompatibility with various substances</b> | No specific information is available in our database regarding the reactivity of this material in presence of various other materials. |
| <b>Corrosivity</b>                             | Non-corrosive in presence of glass.  |
| <b>Special Remarks on Reactivity</b>           | No additional remark.  |
| <b>Special Remarks on Corrosivity</b>          | No additional remark.  |
| <b>Polymerization</b>                          | No.  |

**Section 11. Toxicological Information**

|  |   |
|--|---|
| Routes of Entry                                  | Ingestion.  |
| Toxicity to Animals                              | LD50: Not available.<br>LC50: Not available   |
| Chronic Effects on Humans                        | The substance is toxic to blood, kidneys, liver. Toxicity of the product to the reproductive system: Not available.                           |
| Other Toxic Effects on Humans                    | Slightly dangerous to dangerous in case of ingestion<br>Very slightly to slightly dangerous in case of eye contact (irritant), of inhalation. |
| Special Remarks on Toxicity to Animals           | No additional remark.   |
| Special Remarks on Chronic Effects on Humans     | No additional remark.   |
| Special Remarks on other Toxic Effects on Humans | No additional remark.   |

**Section 12. Ecological Information**

|   |   |
|---|---|
| Ecotoxicity                                       | Not available.  |
| BOD5 and COD                                      | Not available.  |
| Products of Biodegradation                        | Some metallic oxides.   |
| Toxicity of the Products of Biodegradation        | The products of degradation are as toxic as the original product. |
| Special Remarks on the Products of Biodegradation | No additional remark.   |

**Section 13. Disposal Considerations**

|                |  |
|----------------|--|
| Waste Disposal | Recycle to process, if possible. Consult your local or regional authorities. |
|----------------|--|

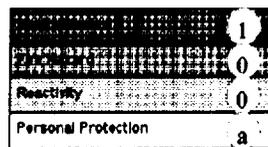
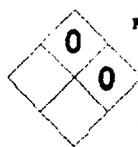
**Section 14. Transport Information**

|                                  |   |
|----------------------------------|---|
| DOT Classification               | Not a DOT controlled material (United States).                                      |
| Identification                   | Not applicable (PIN and PG).  |
| Special Provisions for Transport | Not applicable.   |
| DOT (Pictograms)                 |  |

**Section 15. Other Regulatory Information and Pictograms**

|                                    |   |
|------------------------------------|---|
| Federal and State Regulations      | The following product(s) is (are) listed on TSCA: <b>Ferric subsulfate</b>  |
| California Proposition 65 Warnings | <p><b>WARNING: This product contains a chemical known to the State of California to cause cancer.</b><br/>Chemical ingredient(s) requiring this warning:</p> <p>NONE</p> <p><b>WARNING: This product contains a chemical known to the State of California to cause birth defects or other reproductive harm.</b><br/>Chemical ingredient(s) requiring this warning:</p> <p>NONE</p> |
| Other Regulations                  | OSHA: Hazardous by definition of Hazard Communication Standard (29 CFR 1910.1200).  |

Continued on Next Page

|  |   |  |
|--|---|--|
| <p><b>Other Classifications</b></p>    | <p>WHMIS (Canada) Not controlled under WHMIS (Canada).</p>  |  |
|  | <p>DSCL (EEC) Not controlled under DSCL (Europe)</p>  |  |
| <p>HMIS (U.S.A.)</p>                   |    | <p>National Fire Protection Association (U.S.A.)</p>  <p>Flammability<br/>Health<br/>Reactivity<br/>Specific hazard</p> |
| <p>WHMIS (Canada)<br/>(Pictograms)</p> |    |  |
| <p>DSCL (Europe)<br/>(Pictograms)</p>  |    |  |
| <p>TDG (Canada)<br/>(Pictograms)</p>   |    |  |
| <p>ADR (Europe)<br/>(Pictograms)</p>   |    |  |
| <p>Protective Equipment</p>            |  <p>Lab coat</p><br> <p>Safety glasses.</p> |  |

|   |   |
|---|---|
| <p><b>Section 16. Other Information</b></p>   |   |
| <p>Catalog Number(s)</p>  | <p>F1042</p>                                      |
| <p>References</p>   | <p>Not available.</p>                             |
| <p>Other Special Considerations</p>   | <p>No additional remark.</p>                      |
| <p>Validated by E. Brull on 9/26/97.</p>  | <p>Verified by E. Brull.<br/>Printed 9/29/97.</p> |
| <p>Emergency phone: (310)516-8000</p>   |   |
| <p><b>Notice to Reader</b><br/> <i>All chemicals may pose unknown hazards and should be used with caution. This Material Safety Data Sheet (MSDS) applies only to the material as packaged. If this product is combined with other materials, deteriorates, or becomes contaminated, it may pose hazards not mentioned in this MSDS. It shall be the user's responsibility to develop proper methods of handling and personal protection based on the actual conditions of use. While this MSDS is based on technical data judged to be reliable, Spectrum Quality Products, Inc. assumes no responsibility for the completeness or accuracy of the information contained herein.</i></p> |   |

# Material Safety Data Sheet

|                 |      |                               |
|-----------------|------|-------------------------------|
| NFPA            | HMIS | Personal Protective Equipment |
|                 |      |                               |
| See Section 15. |      |                               |

| Section 1. Chemical Product and Company Identification  |  | Page Number: 1 |
|---|--|----------------|
| <b>Common Name/<br/>Trade Name</b> Ferric subsulfate Solution   | <b>Code</b> F3155  |                |
| <b>Manufacturer</b> SPECTRUM CHEMICAL MFG. CORP.<br>14422 SOUTH SAN PEDRO STREET<br>GARDENA, CALIFORNIA 90248 | <b>CAS#</b> Not applicable.  |                |
| <b>Commercial Name(s)</b> Monsel's Solution   | <b>RTECS</b> Not applicable.   |                |
| <b>Synonym</b> Not available.   | <b>TSCA</b> All the ingredients are on the TSCA list   |                |
| <b>Chemical Name</b> Not applicable.  | <b>CI#</b> Not applicable.   |                |
| <b>Chemical Family</b> Salt.  | <b>IN CASE OF EMERGENCY</b><br><b>CHEMTREC (24hr) 800-424-9300</b><br><br>Emergency phone: (310)516-8000 |                |
| <b>Chemical Formula</b> Not applicable  |  |                |
| <b>Supplier</b> SPECTRUM QUALITY PRODUCTS, INC.<br>14422 SOUTH SAN PEDRO STREET<br>GARDENA, CA 90248          |  |                |

| Section 2. Composition and Information on Ingredients  |           |                          |                           |                           |             |
|--|-----------|--------------------------|---------------------------|---------------------------|-------------|
| Name   | CAS #     | Exposure Limits          |                           |                           | % by Weight |
|  |           | TWA (mg/m <sup>3</sup> ) | STEL (mg/m <sup>3</sup> ) | CEIL (mg/m <sup>3</sup> ) |             |
| Ferric subsulfate  | 1310-45-8 | 1                        |                           |                           | 20-22       |
| Water  | 7732-18-5 |                          |                           |                           | 78-80       |
| <b>Toxicological Data on Ingredients</b> Ferric subsulfate<br>LD50: Not available.<br>LC50: Not available. |           |                          |                           |                           |             |

| Section 3. Hazards Identification       |  |
|---|--|
| <b>Potential Acute Health Effects</b>   | Very slightly to slightly dangerous in case of eye contact (irritant), of ingestion, of inhalation. Not dangerous in case of skin contact (non-corrosive for skin, non-irritant for skin, non-sensitizer for skin, non-permeator by skin).   |
| <b>Potential Chronic Health Effects</b> | Very slightly to slightly dangerous in case of eye contact (irritant), of inhalation. Not dangerous in case of skin contact (non-corrosive for skin, non-irritant for skin, non-sensitizer for skin, non-permeator by skin), of ingestion.<br><b>CARCINOGENIC EFFECTS:</b> Not available. <b>MUTAGENIC EFFECTS:</b> Not available. <b>TERATOGENIC EFFECTS:</b> Not available. The substance is toxic to blood, kidneys, liver. Toxicity of the product to the reproductive system: Not available. Repeated or prolonged exposure to the substance can produce target organs damage.<br><b>WARNING:</b> This product contains a chemical known to the State of California to cause cancer. Chemical ingredient(s) requiring this warning:<br><br>NONE |

Continued on Next Page

**WARNING:** This product contains a chemical known to the State of California to cause birth defects or other reproductive harm.

Chemical ingredient(s) requiring this warning:

NONE

**Section 4. First Aid Measures**

|                             |  |
|-----------------------------|--|
| <b>Eye Contact</b>          | IMMEDIATELY flush eyes with running water for at least 15 minutes, keeping eyelids open. COLD water may be used.   |
| <b>Skin Contact</b>         | NO known EFFECT according to our database.   |
| <b>Serious Skin Contact</b> | No additional information.   |
| <b>Inhalation</b>           | Allow the victim to rest in a well ventilated area. Seek immediate medical attention.  |
| <b>Serious Inhalation</b>   | No additional information.   |
| <b>Ingestion</b>            | Remove dentures if any. Have conscious person drink several glasses of water or milk. INDUCE VOMITING by sticking finger in throat. Lower the head so that the vomit will not reenter the mouth and throat. NEVER give an unconscious person anything to ingest. Seek medical attention. |
| <b>Serious Ingestion</b>    | No additional information.   |

**Section 5. Fire and Explosion Data**

|  |  |
|--|--|
| <b>Flammability of the Product</b>                         | Non-flammable.   |
| <b>Auto-Ignition Temperature</b>                           | Not applicable.  |
| <b>Flash Points</b>  | Not applicable.  |
| <b>Flammable Limits</b>                                    | Not applicable.  |
| <b>Products of Combustion</b>                              | Not applicable.  |
| <b>Fire Hazards in Presence of Various Substances</b>      | Not applicable.  |
| <b>Explosion Hazards in Presence of Various Substances</b> | Risks of explosion of the product in presence of mechanical impact: Not available<br>Risks of explosion of the product in presence of static discharge: Not available.<br>No specific information is available in our database regarding the product's risks of explosion in the presence of various materials |
| <b>Fire Fighting Media and Instructions</b>                | Non-flammable.   |
| <b>Special Remarks on Fire Hazards</b>                     | No additional remark.  |
| <b>Special Remarks on Explosion Hazards</b>                | No additional remark.  |

**Section 6. Accidental Release Measures**

|                    |  |
|--------------------|--|
| <b>Small Spill</b> | Dilute with water and mop up, or absorb with an inert DRY material and place in an appropriate waste disposal container. If necessary: Neutralize the residue with a dilute solution of sodium carbonate. Finish cleaning by spreading water on the contaminated surface and dispose of according to local and regional authority requirements.                                    |
| <b>Large Spill</b> | Our database contains no additional information in case of a spill and/or a leak of the product. Absorb with an inert material and put the spilled material in an appropriate waste disposal. Neutralize the residue with a dilute solution of sodium carbonate. Finish cleaning by spreading water on the contaminated surface and allow to evacuate through the sanitary system. |

**Continued on Next Page**

**Section 7. Handling and Storage**

|             |   |
|-------------|---|
| Precautions | No specific safety phrase has been found applicable for this product.   |
| Storage     | No specific storage is required. Use shelves or cabinets sturdy enough to bear the weight of the chemicals. Be sure that it is not necessary to strain to reach materials, and that shelves are not overloaded. |

**Section 8. Exposure Controls/Personal Protection**

|  |   |
|--|---|
| Engineering Controls                         | Provide exhaust ventilation or other engineering controls to keep the airborne concentrations of vapors below their respective threshold limit value.                                     |
| Personal Protection                          | Safety glasses. Lab coat. Gloves.   |
| Personal Protection in Case of a Large Spill | Splash goggles. Full suit. Boots. Gloves. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.                                       |
| Exposure Limits                              | Ferric subsulfate<br>TWA: 1 (mg/m <sup>3</sup> ) from OSHA/NIOSH [1993]<br>TWA: 1 (mg/m <sup>3</sup> ) from ACGIH [1993]<br><br>Consult local authorities for acceptable exposure limits. |

**Section 9. Physical and Chemical Properties**

|                               |  |       |               |
|-------------------------------|--|-------|---------------|
| Physical state and appearance | Liquid.  | Odor  | Slight.       |
| Molecular Weight              | Not applicable.                                  | Taste | Strong.       |
| pH (1% soln/water)            | 4  | Color | Brownish-red. |
| Boiling Point                 | 100°C (212°F)                                    |       |               |
| Melting Point                 | Not available.                                   |       |               |
| Critical Temperature          | Not available.                                   |       |               |
| Specific Gravity              | 1.58 (Water = 1)                                 |       |               |
| Vapor Pressure                | 17.535 mm of Hg (@ 20°C) based on data for Water |       |               |
| Vapor Density                 | 0.62 (Air = 1) based on data for Water           |       |               |
| Volatility                    | Not available.                                   |       |               |
| Odor Threshold                | Not available.                                   |       |               |
| Water/Oil Dist. Coeff.        | Not available.                                   |       |               |
| Ionicity (in Water)           | Not available.                                   |       |               |
| Dispersion Properties         | See solubility in water.                         |       |               |
| Solubility                    | Easily soluble in cold water, hot water.         |       |               |

**Section 10. Stability and Reactivity Data**

|   |  |
|---|--|
| Stability                               | The product is stable.   |
| Instability Temperature                 | Not available.   |
| Conditions of Instability               | No additional remark.  |
| Incompatibility with various substances | No specific information is available in our database regarding the reactivity of this material in presence of various other materials. |
| Corrosivity                             | Non-corrosive in presence of glass.  |
| Special Remarks on Reactivity           | No additional remark.  |
| Special Remarks on Corrosivity          | No additional remark.  |
| Polymerization                          | Not available.   |

Continued on Next Page

**Section 11. Toxicological Information**

|  |  |
|--|--|
| Routes of Entry                                  | Ingestion.   |
| Toxicity to Animals                              | LD50: Not available<br>LC50: Not available   |
| Chronic Effects on Humans                        | The substance is toxic to blood, kidneys, liver. Toxicity of the product to the reproductive system: Not available.  |
| Other Toxic Effects on Humans                    | Very slightly to slightly dangerous in case of eye contact (irritant), of ingestion, of inhalation<br>Not dangerous in case of skin contact (non-corrosive for skin, non-irritant for skin, non-sensitizer for skin, non-permeator by skin). |
| Special Remarks on Toxicity to Animals           | No additional remark.  |
| Special Remarks on Chronic Effects on Humans     | No additional remark.  |
| Special Remarks on other Toxic Effects on Humans | No additional remark.  |

**Section 12. Ecological Information**

|   |   |
|---|---|
| Ecotoxicity                                       | Not available.  |
| BOD5 and COD                                      | Not available.  |
| Products of Biodegradation                        | Some metallic oxides.   |
| Toxicity of the Products of Biodegradation        | The product itself and its products of degradation are not toxic. |
| Special Remarks on the Products of Biodegradation | No additional remark.   |

**Section 13. Disposal Considerations**

|                |  |
|----------------|--|
| Waste Disposal | Recycle to process, if possible. Consult your local or regional authorities. |
|----------------|--|

**Section 14. Transport Information**

|                                  |   |
|----------------------------------|---|
| DOT Classification               | Not a DOT controlled material (United States).                                      |
| Identification                   | Not applicable (PIN and PG).  |
| Special Provisions for Transport | Not applicable.   |
| DOT (Pictograms)                 |  |

**Section 15. Other Regulatory Information and Pictograms**

|                                    |  |
|------------------------------------|--|
| Federal and State Regulations      | The following product(s) is (are) listed on TSCA: Ferric subsulfate, Water   |
| California Proposition 65 Warnings | WARNING: This product contains a chemical known to the State of California to cause cancer.<br>Chemical ingredient(s) requiring this warning:<br><br>NONE<br><br>WARNING: This product contains a chemical known to the State of California to cause birth defects or other reproductive harm.<br>Chemical ingredient(s) requiring this warning:<br><br>NONE |
| Other Regulations                  | OSHA: Hazardous by definition of Hazard Communication Standard (29 CFR 1910.1200).   |

Continued on Next Page

|                       |                |                                      |
|-----------------------|----------------|--------------------------------------|
| Other Classifications | WHMIS (Canada) | Not controlled under WHMIS (Canada). |
|                       | DSCL (EEC)     | Not controlled under DSCL (Europe)   |

|               |  |  |
|---------------|--|--|
| HMIS (U.S.A.) |  | National Fire Protection Association (U.S.A.)<br>Health<br>Reactivity<br>Specific hazard |
|---------------|--|--|

|                             |  |
|-----------------------------|--|
| WHMIS (Canada) (Pictograms) |  |
|-----------------------------|--|

|                            |  |
|----------------------------|--|
| DSCL (Europe) (Pictograms) |  |
|----------------------------|--|

|                           |  |
|---------------------------|--|
| TDG (Canada) (Pictograms) |  |
|---------------------------|--|

|                           |  |
|---------------------------|--|
| ADR (Europe) (Pictograms) |  |
|---------------------------|--|

|                      |  |                 |
|----------------------|--|-----------------|
| Protective Equipment |  | Gloves.         |
|                      |  | Lab coat.       |
|                      |  | Safety glasses. |

**Section 16. Other Information**

|                                   |   |
|-----------------------------------|---|
| Catalog Number(s)                 | FE107                                     |
| References                        | Not available.                            |
| Other Special Considerations      | No additional remark.                     |
| Validated by E. Brull on 9/26/97. | Verified by E. Brull.<br>Printed 9/29/97. |
| Emergency phone: (310)516-8000    |   |

**Notice to Reader**  
 All chemicals may pose unknown hazards and should be used with caution. This Material Safety Data Sheet (MSDS) applies only to the material as packaged. If this product is combined with other materials, deteriorates, or becomes contaminated, it may pose hazards not mentioned in this MSDS. It shall be the user's responsibility to develop proper methods of handling and personal protection based on the actual conditions of use. While this MSDS is based on technical data judged to be reliable, Spectrum Quality Products, Inc. assumes no responsibility for the completeness or accuracy of the information contained herein.

and titrate with 0.1 N potassium permanganate until a permanent pink color is produced. Each cc. of 0.1 N potassium permanganate corresponds to 15.19 mg. of FeSO<sub>4</sub>. This assay is explained in the chapter on *Official Assays*.  
Storage—Preserve the salt in well-closed containers.

**Uses**—This salt is more stable in air than the fully hydrated Ferrous Sulfate, and is more adaptable for making capsules, pills, and tablets.

**Usual Dose**—0.2 Gm. (approximately 3 grains).

**Ferrous Sulfate Syrup U. S. P. Syrupus Ferri Sulfatis**

[Sp. Jarabe de Sulfato Ferroso]

Ferrous Sulfate Syrup contains, in each 100 cc., not less than 3.75 Gm. and not more than 4.25 Gm. of FeSO<sub>4</sub>·7H<sub>2</sub>O.

|   | Metric   | Alternative        |
|---|----------|--------------------|
| Ferrous Sulfate                         | 40 Gm.   | 1 oz. av. 147 gr.  |
| Citric Acid                             | 2.1 Gm.  | 31 gr.             |
| Peppermint Spirit                       | 2 cc.    | 31 min             |
| Sucrose                                 | 825 Gm.  | 27 oz. av. 236 gr. |
| Distilled Water, a sufficient quantity, |          |                    |
| To make                                 | 1000 cc. | 2 pints            |

Dissolve the ferrous sulfate, the citric acid, the peppermint spirit, and 200 Gm. of sucrose in 450 cc. of distilled water; and filter the solution until clear. Then dissolve the remainder of the sucrose in the clear filtrate, and add sufficient distilled water to make 1000 cc. Mix well and strain, if necessary, through a pledget of cotton.

**Assay**—Transfer 25 cc. of Ferrous Sulfate Syrup, accurately measured, to a 250-cc. Erlenmeyer flask. Add 15 cc. of diluted sulfuric acid and 100 cc. of water, and shake well. Titrate with 0.1 N ceric sulfate, using orthophenanthroline T.S. as the indicator. Each cc. of 0.1 N ceric sulfate is equivalent to 27.80 mg. of FeSO<sub>4</sub>·7H<sub>2</sub>O. This assay is explained in the chapter on *Official Assays*.  
Storage—Preserve this Syrup in tight containers.

**Uses**—See *Ferrous Sulfate*.

**Usual Dose**—8 cc. (approximately 2 fluidrachms).

**Ferrous Sulfate Tablets U. S. P. Tabellæ Ferri Sulfatis**

[Sp. Tabletæ de Sulfato Ferroso]

Ferrous Sulfate Tablets contain not less than 95 per cent and not more than 110 per cent of the labeled amount of FeSO<sub>4</sub>·7H<sub>2</sub>O. An equivalent amount of exsiccated ferrous sulfate may be used in place of FeSO<sub>4</sub>·7H<sub>2</sub>O in preparing Ferrous Sulfate Tablets.

For tests for *Identification* and the *Weight variation* requirements, see the U. S. P.

**Assay**—Weigh a counted number of not less than 20 Ferrous Sulfate Tablets, and crush them well without appreciable loss. Weigh accurately in a beaker a portion of the crushed Tablets, equivalent to about 500 mg. of ferrous sulfate, and dissolve in a mixture of 20 cc. of diluted sulfuric acid and 80 cc. of freshly boiled and cooled water. Filter the solution rapidly as soon as all soluble ingredients in the tablets are dissolved, and wash the beaker and filter with small portions of a mixture of 20 cc. of diluted sulfuric acid and 80 cc. of water. Immediately titrate the combined filtrate and washings with 0.1 N ceric sulfate, using orthophenanthroline T.S. as the indicator. Each cc. of 0.1 N ceric sulfate is equivalent to 27.80 mg. of FeSO<sub>4</sub>·7H<sub>2</sub>O. This assay is explained in the chapter on *Official Assays*.  
Storage—To minimize oxidation, these tablets should be kept in tight containers.

**Usual Dose**—0.3 Gm. (approximately 5 grains) of Ferrous Sulfate.

**Unofficial Inorganic Iron Compounds**

- Ferric Ammonium Sulfate, Ferric Alum**—An official reagent.
- Ferric Chloride, Iron Perchloride [FeCl<sub>3</sub>·6H<sub>2</sub>O]**—An official reagent.
- Ferric Ferrocyanide, Fe<sub>4</sub>[Fe(CN)<sub>6</sub>]<sub>3</sub>**—Commonly called *Prussian blue*. A dark blue powder, insoluble in water. **Uses**: a pigment in paints, in inks, and in bluing. Formerly used in medicine as a tonic. **Dose**: 0.12 to 0.3 Gm. (2 to 5 grains).
- Ferric Ferrocyanide, Soluble, Soluble Iron Ferrocyanide** [approximately KFe[Fe(CN)<sub>6</sub>]<sub>3</sub>·H<sub>2</sub>O]—A blue powder, soluble in water, forming a colloidal solution.
- Ferric Fluoride [FeF<sub>3</sub>·H<sub>2</sub>O]**—White to slightly yellow, crystalline powder. Slightly soluble in water or in alcohol.
- Ferric Hydroxide, Antidotum Fuchsi, Hydrated Ferric Oxide**—See *Magma of Ferric Hydroxide* (page 248).
- Ferric Nitrate [Fe(NO<sub>3</sub>)<sub>3</sub>]**—Grayish white crystals; soluble in water.

**Uses**: a mordant in dyeing and in calico-printing; also a tonic and astringent.  
**Ferric Oxide, Saccharated N. F. VII**—The following directions were given:

Dissolve 11 Gm. of monohydrated sodium carbonate in 150 cc. distilled water. Dilute 30 Gm. of ferric chloride solution with 150 cc. of distilled water and gradually add, with constant stirring, to the carbonate solution. Decant the supernatant liquid and wash the precipitate with distilled water until a portion of the washings, when diluted with 5 volumes of distilled water, give only a slight opalescence with silver nitrate T.S. Collect the precipitate on a cloth strainer, transfer the mass to a porcelain dish on a water bath, and add 50 Gm. of sucrose and a sufficient quantity (not more than 5 cc.) of a 15 per cent solution of sodium hydroxide to produce a clear solution. Evaporate the mixture to dryness upon a water bath and, if necessary, add sufficient powdered sucrose to make the product weigh 100 Gm. When so prepared it contains about 3 per cent of iron [Fe] corresponding to about 4.5 per cent of ferric oxide.

It occurs as a brown powder which is soluble in water but insoluble in alcohol. The iron in this preparation is non-ionic and it does not respond to some of the usual reactions for iron. **Uses**: a hematinic. **Dose**: 2 Gm. (30 grains) corresponding to 60 mg. of Fe. Certain specially prepared solutions of saccharated ferric oxide may be administered intravenously, and are currently receiving trial for the treatment of refractory hypochromic anemias.

**Ferric Phosphate [FePO<sub>4</sub>·4H<sub>2</sub>O]**—A nearly white or slightly yellow, crystalline powder. Insoluble in water or in acetic acid; soluble in mineral acid. **Uses**: source of iron for the enrichment of foods.

**Ferric Pyrophosphate [Fe<sub>4</sub>(P<sub>2</sub>O<sub>7</sub>)<sub>3</sub>·9H<sub>2</sub>O]**—Nearly white to slightly yellow, crystalline powder. Insoluble in water; soluble in mineral acids; also soluble when freshly prepared, in an excess of alkali citrate, forming green solutions.

**Ferric Pyrophosphate, Soluble**—This is a complex salt of sodium ferritropyphosphate. It is made by the process described for *Soluble Ferric Phosphate*, replacing the sodium phosphate with sodium pyrophosphate. It contains 11 to 13 per cent of iron. The iron in this phosphate is, like that in *Soluble Ferric Phosphate*, non-ionic. It occurs as bright green scales or as granules. It is freely soluble in water but insoluble in alcohol. **Uses**: a hematinic. **Dose**: 0.25 Gm. (4 grains).

**Ferric Subsulfate [approximately Fe<sub>4</sub>(SO<sub>4</sub>)<sub>3</sub>(OH)<sub>2</sub>]**—Yellow, somewhat hygroscopic powder, very slowly and usually incompletely soluble in water; insoluble in alcohol. **Uses**: a styptic, and a mordant in textile dyeing.

**Ferric Sulfate [Fe<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub>]**—Grayish white, very hygroscopic powder. Slowly soluble in water, sparingly soluble in alcohol. **Uses**: employed in dyeing, in the manufacture of Prussian blue and inks, and in water purification.

**Ferrous Ammonium Sulfate**—An official reagent.

**Ferrous Bromide [FeBr<sub>2</sub>]**—A yellowish, deliquescent crystalline powder. Soluble in water. **Uses**: alterative and tonic. **Dose**: 0.06 to 0.2 Gm. (1 to 3 grains).

**Ferrous Chloride [FeCl<sub>2</sub>·H<sub>2</sub>O]**—Pale green, deliquescent crystals, or crystalline powder. Oxidizes on exposure to air. Soluble in 1 part water acidulated with hydrochloric acid; incompletely soluble in alcohol. **Uses**: astringent in gargles; also a mordant in printing fabrics and in dyeing.

**Ferrous Iodide [FeI<sub>2</sub>·4H<sub>2</sub>O]**—Almost black, very deliquescent masses. Decomposes rapidly in air with liberation of iodine. Freely soluble in cold water, decomposed by hot water; also soluble in alcohol. **Uses**: an alterative and tonic, generally given in pills or capsules.

**Ferrous Phosphate [Fe<sub>2</sub>(PO<sub>4</sub>)<sub>2</sub>·8H<sub>2</sub>O]**—On account of rapid oxidation in air the article of commerce contains basic ferric phosphate. A grayish blue powder. Insoluble in water, soluble in mineral acid. **Uses**: a hematinic; also used in coloring ceramics. **Dose**: 0.3 to 0.5 Gm. (5 to 8 grains).

**Ferrous Sulfide [FeS]**—An official reagent.

**Inorganic Iron Specialties**

*Note*—The following preparations, containing iron per se, or iron supplemented with vitamins and other substances, are used as hematinics and dietary supplements. The dose varies with the requirements of the individual.

- Aminoferin (J. T. Lloyd)**—Liquid containing iron, aminoacetic acid, and thiamine hydrochloride in an oat menstruum.
- Arsenoferratose (Rare-Galen)**—Elixir, each fluidounce containing sodium ferrialbuminate sufficient to furnish 235 mg. iron, and 0.9 mg. arsenic; tablets, each containing sodium ferrialbuminate to furnish 16 mg. iron, and 0.09 mg. arsenic.
- Ascoferin (Dorsey)**—Capsules, each containing 0.325 Gm. ferrous sulfate and 50 mg. ascorbic acid.
- B Ferrated (Upjohn)**—Elixir, each fluidounce containing 1.3 Gm. ferrous sulfate with vitamin B complex supplement.
- Befolex (Central)**—Tablets, each containing 19.4 mg. ferrous sulfate with folic acid and vitamin B complex factors.
- Beofer (Rexall)**—Elixir or tablets, each fluidounce of the elixir containing 3 gr. ferrous sulfate, 2 mg. riboflavin, and 1 mg. thiamine hydrochloride; each tablet containing 3 gr. ferrous sulfate, 5 mg. nicotinic acid, 0.08 mg. pyridoxine hydrochloride, 0.6 mg. riboflavin, and 120 U. S. P. units vitamin B<sub>1</sub>.
- Betacuron (Lakeside)**—Liquid, each 30 cc. containing 274 mg. iron peptonate, 15.9 mg. copper gluconate, with vitamin B factors.
- Betaferum (Hart Drug)**—Elixir or tablets, each fluidounce of elixir containing 20 gr. ferrous sulfate and 3.6 mg. thiamine hydrochloride; each tablet containing 3 gr. exsiccated ferrous sulfate and 1.0 mg. thiamine hydrochloride.
- Betaron (Warren-Teed)**—Syrup, each fluidounce containing 1 Gm. ferrous sulfate and 3 mg. thiamine hydrochloride.
- Biatron (National Drug)**—Elixir, each fluidounce containing 4 gr. green iron and ammonium citrates, 5 per cent alcohol, 4 gr. calcium

|                                      |                                   |        |
|--------------------------------------|-----------------------------------|--------|
| Dithymol Diiodide (Thymol Iodide)    | $(C_{10}H_{12}O)_2I_2$            | 0-16   |
| <b>Dysprosium</b>                    | Dy                                | 550.03 |
| Emetine                              | $C_{15}H_{22}O_2N$                | 162.5  |
| " Hydrochloride, Anhydrous           | $C_{30}H_{44}O_4N_2 \cdot 2HCl$   | 248.19 |
| Epinephrine, Hydrated                | $C_9H_{13}O_3N + \frac{1}{2}H_2O$ | 569.31 |
| <b>Erbium</b>                        | Er                                | 192.12 |
| Erythrol Tetranitrate                | $C_4H_6(NO_3)_4$                  | 167.7  |
| Ether (Ethyl Oxide)                  | $(C_2H_5)_2O$                     | 302.09 |
| Ethyl Acetate                        | $C_2H_5C_2H_3O_2$                 | 74.08  |
| " Carbamate                          | $CO(OC_2H_5)NH_2$                 | 88.06  |
| " Chloride                           | $C_2H_5Cl$                        | 89.07  |
| " Hydroxide (Ethyl Alcohol)          | $C_2H_5OH$                        | 64.50  |
| Ethylmorphine Hydrochloride          | $C_{19}H_{23}O_3NHCl + 2H_2O$     | 46.05  |
| " Anhydrous                          | $C_{19}H_{23}O_3NHCl$             | 385.69 |
| Ethyl Nitrite                        | $C_2H_5NO_2$                      | 349.66 |
| " Oxide (Ether)                      | $(C_2H_5)_2O$                     | 75.05  |
| Eucaïne (Beta)                       | $C_{18}H_{21}O_2NHCl + H_2O$      | 74.08  |
| Eucalyptol (Cineol)                  | $C_{10}H_{18}O$                   | 301.66 |
| Eugenol                              | $C_{10}H_{12}O_2$                 | 154.14 |
| <b>Europium</b>                      | Eu                                | 164.10 |
| Ferric Acetate                       | $Fe(C_2H_3O_2)_3$                 | 152.0  |
| " Ammonium Sulphate                  | $FeNH_4(SO_4)_2 + 12H_2O$         | 232.91 |
| " Anhydrous                          | $FeNH_4(SO_4)_2$                  | 482.21 |
| " Chloride                           | $FeCl_3 + 6H_2O$                  | 266.02 |
| " Anhydrous                          | $FeCl_3$                          | 270.32 |
| " Hydroxide                          | $Fe(OH)_3$                        | 162.22 |
| " Hypophosphite                      | $Fe(PH_2O_2)_3$                   | 106.86 |
| " Nitrate                            | $Fe(NO_3)_3$                      | 251.01 |
| " Oxide                              | $Fe_2O_3$                         | 241.87 |
| " Phosphate (normal, not U.S.P.)     | $FePO_4$                          | 159.68 |
| " Pyrophosphate (normal, not U.S.P.) | $Fe_4(P_2O_7)_3$                  | 150.88 |
| " <u>Subsulphate (variable)</u>      |                                   | 745.60 |
| " Sulphate (Tersulphate)             | $Fe_2(SO_4)_3$                    | 399.89 |
| Ferrous Bromide                      | $FeBr_2 + 6H_2O$                  | 323.78 |
| " Anhydrous                          | $FeBr_2$                          | 215.68 |
| " Carbonate                          | $FeCO_3$                          | 115.84 |
| " Iodide                             | $FeI_2$                           | 309.68 |
| " Lactate                            | $Fe(C_3H_5O_3)_2 + 3H_2O$         | 287.97 |
| " Anhydrous                          | $Fe(C_3H_5O_3)_2$                 | 233.92 |
| " Oxide                              | $FeO$                             | 71.84  |
| " Sulphate                           | $FeSO_4 + 7H_2O$                  | 278.02 |
| " Anhydrous                          | $FeSO_4$                          | 151.91 |
| " Exsiccated (approximately)         | $2FeSO_4 + 3H_2O$                 | 357.87 |
| " Sulphide                           | $FeS$                             | 87.91  |
| <b>Ferrum</b>                        | Fe                                | 55.84  |
| Fluorescein (Resorcinolphthalein)    | $C_{20}H_{12}O_5$                 | 332.10 |
| <b>Fluorine</b>                      | F                                 | 19.0   |

**Assay**—Dissolve about 1 Gm. of Soluble Ferric Phosphate, accurately weighed, in 25 ml. of water and 5 ml. of hydrochloric acid in a glass-stoppered flask; add 4 Gm. of potassium iodide, securely stopper the flask, and allow the mixture to stand 15 minutes; dilute with 50 ml. of water, and titrate the liberated iodine with 0.1 *N* sodium thiosulfate, using starch T.S. as the indicator. Perform a blank determination with the same quantities of the reagents and in the same manner and make any necessary correction. Each ml. of 0.1 *N* sodium thiosulfate is equivalent to 5.585 mg. of Fe.

**Packaging and storage**—Preserve Soluble Ferric Phosphate in well-closed, light-resistant containers.

**CATEGORY**—Hematinic.

**USUAL DOSE**—250 mg. (approximately 4 grains).

### Ferric Subsulfate Solution

## FERRIC SUBSULFATE SOLUTION

Monsel's Solution

Basic Ferric Sulfate Solution

Ferric Subsulfate Solution is a water solution containing, in each 100 ml., basic ferric sulfate equivalent to not less than 20 Gm. and not more than 22 Gm. of Fe.

|  |          |
|--|----------|
| Ferrous Sulfate . . . . .                    | 1045 Gm. |
| Sulfuric Acid . . . . .                      | 55 ml.   |
| Nitric Acid,                                 |          |
| Purified Water, each, a sufficient quantity, |          |
| To make . . . . .                            | 1000 ml. |

Add the sulfuric acid to 800 ml. of purified water in a suitable porcelain dish, and heat the mixture nearly to 100°; then add 75 ml. of nitric acid, and mix well. Divide the ferrous sulfate, coarsely powdered, into 4 approximately equal portions, and add these portions one at a time to the hot liquid, stirring after each addition until effervescence ceases. If, after the ferrous sulfate has dissolved, the solution has a black color, add nitric acid, a few drops at a time, with heating and stirring, until red fumes cease to be evolved. Boil the solution until it assumes a red color and is free from nitrate, as indicated by the test below, maintaining the volume at about 1000 ml. by the addition of purified water as needed. Cool, and add enough purified water to make the product measure 1000 ml.; filter, if necessary, until the product is clear.

**NOTE:** If exposed to low temperatures, crystallization may take place in the Solution. The crystals will redissolve upon warming the Solution.

**Description**—Ferric Subsulfate Solution is a reddish brown liquid, odorless or nearly so, with a sour, strongly astringent taste. Ferric Subsulfate Solution is acid to litmus, and it is affected by light. Its specific gravity is about 1.548.

**A. INGREDIENT NAME:**

**FERRIC SULFATE HYDRATE**

**B. Chemical Name:**

Diiron Trisulfate

**C. Common Name:**

Ferric Sulfate, Iron Persulfate, Iron Sesquisulfate, Iron Sulfate (2:3), Iron (3+) sulfate, Iron Tersulfate, Sulfuric Acid, Iron (3+) Salt (3:2)

**D. Chemical grade or description of the strength, quality, and purity of the ingredient:**

Purity: 73.0 min.

A solution responds to the test for ferric iron and sulfate.

**E. Information about how the ingredient is supplied:**

Grayish-white powder, or Rhombic or Rhombohedral crystals, very hygroscopic, commercial product usually contains about 20% water and is yellowish in color.

**F. Information about recognition of the substance in foreign pharmacopeias:**

**G. Bibliography of available safety and efficacy data including peer reviewed medical literature:**

Fuks, A. B., Holan, G., and Davis, J. M. Ferric sulfate versus dilute formocresol in pulpotomized primary molars: long-term follow up. *Pediatric Dentistry*, 1997; 19(5): 327-330.

Jeansonne, B. G., Boggs, W. S., and Lemon, R. R. Ferric sulfate hemostasis: effect on osseous wound healing. II. With curettage and irrigation. *Journal of Endodontics*, 1993; 19(4): 174-176.

Fei, A. L., Udin, r. d., and Johnson, R. A clinical study of ferric sulfate as a pulpotomy agent in primary teeth. *Pediatric Dentistry*, 1991; 13(6): 327-332.

Shaw, D. H., Krejci, R. F., and Kalkwarf, K. L. Gingival response to retraction by ferric sulfate. *Operative Dentistry*, 1983; 8(4): 142-147.

**H. Information about dosage forms used:**

Solution

**I. Information about strength:**

**J. Information about route of administration:**

**K. Stability data:**

Store at room temperature. Protect from light.  
Stable

**L. Formulations:**

Ferrous Sulphate.....400gm  
Sulphuric Acid.....78gm  
Nitric Acid, Distilled water - a significant quantity.  
\*See file for compounding formulation\*

**M. Miscellaneous Information:**

CERTIFICATE OF QUALITY

30-2267  
# 53569

Product: FERRIC SULFATE, HYDRATE **A**  
Grade: Reagent Grade  
Lot: 2445A23

Appearance: Fine yellow crystalline powder **E**

Mol. Formula:  $Fe_2(SO_4)_3 \cdot xH_2O$

Mol. Weight: 399.88 (anhydrous)

Description:

Assay:

| <u>Minimum</u> | <u>Maximum</u> | <u>Units</u> |
|----------------|----------------|--------------|
| <u>73.0</u>    |                | %            |
|                | 0.02           | %            |
|                | <0.002         | %            |
|                | <0.02          | %            |
|                | <0.005         | %            |
|                | <0.005         | %            |
|                | <0.01          | %            |
|                | <0.1           | %            |

Purity

Insolubles

Chloride (L=0.002)

Ferrous Iron (L=0.02)

Copper (L=0.005)

Zinc (L=0.005)

Nitrate (L=0.01)

Non-precipitables (by NH<sub>3</sub>, L=0.1)

Storage: Store at room temperature. Protect from moisture.

K

✓

10/97

# QUALITY CONTROL REPORT

CHEMICAL NAME.: FERRIC SULFATE HYDRATE

MANUFACTURE LOT NO.: 2036A41

## PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP \_\_\_/BP \_\_\_/MERCK \_\_\_/NF \_\_\_/MART. \_\_\_/CO. SPECS. \_\_\_.

### 1) DESCRIPTION.:

GRAYISH-WHITE POWDER, OR RHOMBIC OR RHOMBOHEDRAL CRYSTALS; VERY HYGROSCOPIC; ~~COMMERCIAL PRODUCT USUALLY CONTAINS ABOUT 20% WATER AND IS YELLOWISH IN COLOR.~~

### 2) SOLUBILITY.:

SLOWLY SOLUBLE IN WATER, RAPIDLY SOLUBLE IN THE PRESENCE OF A TRACE OF  $\text{FeSO}_4$ ; SPARINGLY SOLUBLE IN ALCOHOL; PRACTICALLY INSOLUBLE IN ACETONE, AND ETHYL ACETATE; HYDROLYZED SLOWLY IN AQUEOUS SOLUTIONS.

### 3) MELTING POINT.:

### 4) SPECIFIC GRAVITY.:

### 5) IDENTIFICATION.:

A) A SOLUTION RESPONDS TO THE TEST FOR FERRIC IRON AND SULFATE.

PASSES.: \_\_\_\_\_

FAILS.: \_\_\_\_\_

COMMENTS.:

ANALYST SIGNATURE.: \_\_\_\_\_

DATE.: \_\_\_\_\_

PREPACK TEST.: \_\_\_\_\_

DATE.: \_\_\_\_\_

INITIAL.: \_\_\_\_\_

RETEST.: \_\_\_\_\_

DATE.: \_\_\_\_\_

INITIAL.: \_\_\_\_\_



Use your web browser's "Back" key to return to previous topic.

**Ferric Sulfate Monohydrate**

**\*\*\*\* MATERIAL SAFETY DATA SHEET \*\*\*\***

**Ferric Sulfate Monohydrate**  
45419

**\*\*\*\* SECTION 1 - CHEMICAL PRODUCT AND COMPANY IDENTIFICATION \*\*\*\***

MSDS Name: Ferric Sulfate Monohydrate  
Catalog Numbers:  
S80013

Synonyms:

Diiron Trisulfate; Ferric Sulfate; Iron Persulfate; Iron Sesquisulfate; Iron Sulfate (2:3); Iron (3+) Sulfate; Sulfuric Acid, Iron

Company Identification: Fisher Scientific  
1 Reagent Lane  
Fairlawn, NJ 07410

For information, call: 201-796-7100  
Emergency Number: 201-796-7100  
For CHEMTREC assistance, call: 800-424-9300  
For International CHEMTREC assistance, call: 703-527-3887

**\*\*\*\* SECTION 2 - COMPOSITION, INFORMATION ON INGREDIENTS \*\*\*\***

| CAS#       | Chemical Name               | %   | EINECS#   |
|------------|-----------------------------|-----|-----------|
| 10028-22-5 | Ferric sulfate, monohydrate | 100 | 233-072-9 |

Hazard Symbols: XI  
Risk Phrases: 36/37

**\*\*\*\* SECTION 3 - HAZARDS IDENTIFICATION \*\*\*\***

**EMERGENCY OVERVIEW**

Appearance: yellow-gray.  
Caution! May cause respiratory tract irritation. May cause liver and kidney damage. Causes severe digestive tract irritation with pain, nausea, vomiting and diarrhea. May corrode the digestive tract with hemorrhaging and possible shock.  
Target Organs: None.

**Potential Health Effects**

- Eye: May cause eye irritation.
- Skin: May cause skin irritation.
- Ingestion: May cause severe gastrointestinal tract irritation with nausea,

vomiting and possible burns. May cause liver and kidney damage.  
 Inhalation:  
 May cause respiratory tract irritation.  
 Chronic:  
 No information found.

\*\*\*\* SECTION 4 - FIRST AID MEASURES \*\*\*\*

Eyes:  
 Flush eyes with plenty of water for at least 15 minutes, occasionally lifting the upper and lower lids. Get medical aid immediately.  
 Skin:  
 Get medical aid if irritation develops or persists. Flush skin with plenty of soap and water.  
 Ingestion:  
 If victim is conscious and alert, give 2-4 cupfuls of milk or water. Never give anything by mouth to an unconscious person. Get medical aid immediately.  
 Inhalation:  
 Get medical aid immediately. Remove from exposure to fresh air immediately. If not breathing, give artificial respiration. If breathing is difficult, give oxygen.  
 Notes to Physician:  
 Treat symptomatically and supportively.

\*\*\*\* SECTION 5 - FIRE FIGHTING MEASURES \*\*\*\*

General Information:  
 As in any fire, wear a self-contained breathing apparatus in pressure-demand, MSHA/NIOSH (approved or equivalent), and full protective gear.  
 Extinguishing Media:  
 Use alcohol foam, carbon dioxide, or water spray when fighting fires involving this material.  
 Autoignition Temperature: Not applicable.  
 Flash Point: Not applicable.  
 NFPA Rating: Not published.  
 Explosion Limits, Lower: Not available.  
 Upper: Not available.

\*\*\*\* SECTION 6 - ACCIDENTAL RELEASE MEASURES \*\*\*\*

General Information: Use proper personal protective equipment as indicated in Section 8.  
 Spills/Leaks:  
 Clean up spills immediately, observing precautions in the Protective Equipment section. Sweep up or absorb material, then place into a suitable clean, dry, closed container for disposal.

\*\*\*\* SECTION 7 - HANDLING and STORAGE \*\*\*\*

Handling:  
 Wash thoroughly after handling. Remove contaminated clothing and wash before reuse. Use with adequate ventilation. Discard contaminated shoes.  
 Storage:  
 Store in a cool, dry place. Keep containers tightly closed.

\*\*\*\* SECTION 8 - EXPOSURE CONTROLS, PERSONAL PROTECTION \*\*\*\*

Engineering Controls:  
 Use adequate ventilation to keep airborne concentrations low.

Exposure Limits

| Chemical Name               | ACGIH       | NIOSH       | OSHA - Final PELs |
|-----------------------------|-------------|-------------|-------------------|
| Ferric sulfate, monohydrate | none listed | none listed | none listed       |

OSHA Vacated PELs:  
 Ferric sulfate, monohydrate:  
 No OSHA Vacated PELs are listed for this chemical.

Personal Protective Equipment

Eyes:  
 Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133.

Skin:  
 Wear appropriate protective gloves to prevent skin exposure.

Clothing:  
 Wear appropriate protective clothing to prevent skin exposure.

Respirators:  
 A respiratory protection program that meets OSHA's 29 CFR 1910.134 and ANSI Z88.2 requirements must be followed whenever workplace conditions warrant a respirator's use.

\*\*\*\* SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES \*\*\*\*

Physical State: Solid  
 Appearance: yellow-gray  
 Odor: Odorless.  
 pH: Not available.  
 Vapor Pressure: Negligible.  
 Vapor Density: Not available.  
 Evaporation Rate: Negligible.  
 Viscosity: Not available.  
 Boiling Point: Not applicable.  
 Freezing/Melting Point: Decomposes.  
 Decomposition Temperature: 480 deg C  
 Solubility: Soluble in water.  
 Specific Gravity/Density: 3.097  
 Molecular Formula: Fe2(SO4)3.H2O  
 Molecular Weight: 399.8668

\*\*\*\* SECTION 10 - STABILITY AND REACTIVITY \*\*\*\*

Chemical Stability:  
~~Stable under normal temperatures and pressures.~~  
 Conditions to Avoid:  
 Incompatible materials.  
 Incompatibilities with Other Materials:  
 Corrosive to metals.  
 Hazardous Decomposition Products:  
 Sulfur oxides (SOx), including sulfur oxide and sulfur dioxide.  
 Hazardous Polymerization: Will not occur.

\*\*\*\* SECTION 11 - TOXICOLOGICAL INFORMATION \*\*\*\*

RTECS#:  
 CAS# 10028-22-5: NO8505000  
 LD50/LC50:  
 Not available.  
 Carcinogenicity:  
 Ferric sulfate, monohydrate -  
 Not listed by ACGIH, IARC, NIOSH, NTP, or OSHA.  
 Epidemiology:  
 No data available.  
 Other Studies:  
 No data available.

\*\*\*\* SECTION 12 - ECOLOGICAL INFORMATION \*\*\*\*

Environmental Fate:  
 Not available.

\*\*\*\* SECTION 13 - DISPOSAL CONSIDERATIONS \*\*\*\*

Dispose of in a manner consistent with federal, state, and local regulations.  
 RCRA D-Series Maximum Concentration of Contaminants: Not listed.  
 RCRA D-Series Chronic Toxicity Reference Levels: Not listed.  
 RCRA F-Series: Not listed.  
 RCRA P-Series: Not listed.  
 RCRA U-Series: Not listed.  
 Not listed as a material banned from land disposal according to RCRA.

\*\*\*\* SECTION 14 - TRANSPORT INFORMATION \*\*\*\*

US DOT  
 Shipping Name: CORROSIVE SOLID, ACIDIC, INORGANIC, N.O.S.  
 (SULFURIC ACID)  
 Hazard Class: 8  
 UN Number: UN3260  
 Packing Group: II

IMO  
 No information available.

IATA  
 No information available.

RID/ADR  
 No information available.

Canadian TDG  
 No information available.

\*\*\*\* SECTION 15 - REGULATORY INFORMATION \*\*\*\*

US FEDERAL

TSCA  
 CAS# 10028-22-5 is listed on the TSCA inventory.  
 Health & Safety Reporting List  
 None of the chemicals are on the Health & Safety Reporting List.  
 Chemical Test Rules  
 None of the chemicals in this product are under a Chemical Test Rule.  
 Section 12b  
 None of the chemicals are listed under TSCA Section 12b.  
 TSCA Significant New Use Rule  
 None of the chemicals in this material have a SNUR under TSCA.

SARA

Section 302 (RQ)  
 final RQ = 1000 pounds (454 kg)  
 Section 302 (TPQ)  
 None of the chemicals in this product have a TPQ.  
 Section 313  
 No chemicals are reportable under Section 313.

Clean Air Act:

This material does not contain any hazardous air pollutants.  
 This material does not contain any Class 1 Ozone depleters.  
 This material does not contain any Class 2 Ozone depleters.

Clean Water Act:

CAS# 10028-22-5 is listed as a Hazardous Substance under the CWA.  
 None of the chemicals in this product are listed as Priority  
 Pollutants under the CWA.  
 None of the chemicals in this product are listed as Toxic Pollutants  
 under the CWA.

OSHA:

None of the chemicals in this product are considered highly hazardous  
 by OSHA.

STATE

Ferric sulfate, monohydrate can be found on the following state right  
 to know lists: New Jersey, Pennsylvania, Massachusetts.  
 California No Significant Risk Level:  
 None of the chemicals in this product are listed.

European/International Regulations

European Labeling in Accordance with EC Directives  
 Hazard Symbols: XI  
 Risk Phrases:  
 R 36/37 Irritating to eyes and respiratory system.  
 Safety Phrases:

WGK (Water Danger/Protection)

CAS# 10028-22-5: 1

Canada

CAS# 10028-22-5 is listed on Canada's DSL/NDSL List.

WHMIS: Not available.

CAS# 10028-22-5 is not listed on Canada's Ingredient Disclosure List.

Exposure Limits

CAS# 10028-22-5: OEL-DENMARK:TWA 1 mg(Fe)/m3 JANUARY 1993. OEL-FINLAND:TWA 1 mg(Fe)/m3 JANUARY 1993. OEL-THE NETHERLANDS:TWA 1 mg(Fe)/m3 JANUARY 1993. OEL-SWITZERLAND:TWA 1 mg(Fe)/m3 JANUARY 1993. OEL-UNITED KINGDOM:TWA 1 mg(Fe)/m3;STEL 2 mg(Fe)/m3 JANUARY 1993. OEL IN BULGARIA, COLOMBIA, JORDAN, KOREA check ACGIH TLV. OEL IN NEW ZEALAND, SINGAPORE, VIETNAM check ACGI TLV

\*\*\*\* SECTION 16 - ADDITIONAL INFORMATION \*\*\*\*

MSDS Creation Date: 6/28/1995 Revision #3 Date: 9/02/1997

The information above is believed to be accurate and represents the best information currently available to us. However, we make no warranty of merchantability or any other warranty, express or implied, with respect to such information, and we assume no liability resulting from its use. Users should make their own investigations to determine the suitability of the information for their particular purposes. In no way shall Fisher be liable for any claims, losses, or damages of any third party or for lost profits or any special, indirect, incidental, consequential or exemplary damages, howsoever arising, even if Fisher has been advised of the possibility of such damages.

-----

ite, in clear crystals, *six hundred and*  
*grammes*..... 675 Gm.  
*sixty-five grammes*..... 65 Gm.

r, each, a sufficient quantity,

To make one thousand grammes.... 1000 Gm.

tric Acid to *five hundred (500) cubic centimeters*  
 in a capacious porcelain capsule, heat the mixture  
 (212° F.), then add *sixty-five (65) grammes* of  
 l. Divide the Ferrous Sulphate, coarsely powdered  
 portions, and add these portions, one at a time,  
 stirring after each addition until effervescence ceases.  
 Ferrous Sulphate is dissolved, add a few drops  
 if this causes a further evolution of red fumes.  
 ic Acid, a few drops at a time, until it no longer  
 to be evolved; then boil the Solution until it is  
 and is free from nitrous odor. Lastly, add  
 to make the product weigh *one thousand (1000) grammes*  
 in well-stoppered bottles, in a moderately  
 22° C. or 71.6° F.), protected from light.  
 will sometimes crystallize, forming a semi-solid  
 s occurs, the application of a gentle heat to the  
 condition.

on Ferric Subsulphate is to be dispensed  
 sulphate of Iron has been prescribed by the physician.

ish-brown liquid, odorless or nearly so, of an acid  
 and an acid reaction.

ty: about 1.550 at 15° C. (59° F.).

1 water and alcohol, in all proportions, without decomposition.  
 solution yields a brownish-red precipitate with ammonia water,  
 h potassium ferrocyanide T.S., and a white one, insoluble in  
 id, with barium chloride T.S.

ixing 2 volumes of the Solution with 1 volume of concentrated  
 in a beaker, a semi-solid, white mass will separate on standing  
 n *tersulphate*).

t clear crystal of ferrous sulphate to a cooled mixture of equal  
 concentrated sulphuric acid and a diluted portion of the  
 ould not become brown, nor should there be a brownish  
 d around it (absence of *nitric acid*).

ll portion of the Solution, diluted with about 10 volumes  
 drops of freshly prepared potassium ferricyanide T.S., a  
 color should be produced, without a tinge of greenish-blue  
 of *ferrous salt*).

(76) Gm. of the Solution be introduced into a glass capsule  
 : a capacity of about 100 Cc.), together with 15 Cc. of  
 rochloric acid, and, after the addition of 1 Gm. of  
 xture be kept for half an hour at a temperature of 20° C.

F.), then cooled, and mixed with a few drops of starch T.S., it should require  
 about 27.2 Cc. of decinormal sodium hyposulphite V.S. to discharge the blue  
 or greenish color of the liquid (each Cc. of the volumetric solution indicating  
 0.5 per cent. of metallic iron).

## LIQUOR FERRI TERSULPHATIS.

### SOLUTION OF FERRIC SULPHATE.

An aqueous solution of normal Ferric Sulphate [ $Fe_2(SO_4)_3 = 399.22$ ],  
 containing about 28.7 per cent. of the salt, and corresponding to about  
 per cent. of metallic iron.

Ferrous Sulphate, in clear crystals, *four hundred grammes* 400 Gm.  
 Sulphuric Acid, *seventy-eight grammes*..... 78 Gm.

Nitric Acid,

Distilled Water, each, a sufficient quantity,

To make one thousand grammes.... 1000 Gm.

Add the Sulphuric Acid to *two hundred (200) cubic centimeters* of  
 distilled Water in a capacious porcelain capsule, heat the mixture  
 nearly 100° C. (212° F.), then add *fifty-five (55) grammes* of Nitric  
 acid, and mix well. Divide the Ferrous Sulphate, coarsely powdered,  
 into four equal portions, and add these portions, one at a time, to  
 the hot liquid, stirring after each addition until effervescence ceases.  
 When all of the Ferrous Sulphate is dissolved, add a few drops of  
 Nitric Acid, and, if this causes a further evolution of red fumes, con-  
 tinue to add Nitric Acid, a few drops at a time, until it no longer  
 causes red fumes to be evolved; then boil the Solution until it assumes  
 a reddish-brown color and is free from nitrous odor. Lastly, add  
 enough Distilled Water to make the product weigh *one thousand (1000)*  
*grammes*. Filter, if necessary.

A dark reddish-brown liquid, almost odorless, having an acid, strongly  
 astringent taste, and an acid reaction.

Specific gravity: about 1.320 at 15° C. (59° F.).

Miscible with water and alcohol, in all proportions, without decomposition.

The diluted Solution yields a brownish-red precipitate with ammonia water,  
 a blue one with potassium ferrocyanide T.S., and a white one, insoluble in  
 hydrochloric acid, with barium chloride T.S.

On slowly mixing 2 volumes of the Solution with 1 volume of concentrated  
 sulphuric acid, in a beaker, no solid, white mass will separate on standing  
 (difference from *subsulphate*).

On adding a clear crystal of ferrous sulphate to a cooled mixture of equal  
 volumes of concentrated sulphuric acid and a moderately diluted portion of  
 the Solution, the crystal should not become brown, nor should there be a  
 brownish-black color developed around it (absence of *nitric acid*).

If to a small portion of the Solution, diluted with about 10 volumes of water,  
 a few drops of freshly prepared potassium ferricyanide T.S. be added, a pure  
 brown color should be produced, without a tinge of green or greenish-blue  
 (absence of *ferrous salt*).

|                                      |                                   |        |
|--------------------------------------|-----------------------------------|--------|
| Dithymol Diiodide (Thymol Iodide)    | $(C_{10}H_{12}O)_2I_2$            | 0-16   |
| <b>Dysprosium</b>                    | <b>Dy</b>                         | 550.08 |
| Emetine                              | $C_{15}H_{22}O_2N$                | 162.5  |
| " Hydrochloride, Anhydrous           | $C_{30}H_{44}O_4N_2 \cdot 2HCl$   | 248.19 |
| Epinephrine, Hydrated                | $C_9H_{13}O_3N + \frac{1}{2}H_2O$ | 569.31 |
| <b>Erbium</b>                        | <b>Er</b>                         | 192.12 |
| Erythrol Tetranitrate                | $C_4H_8(NO_3)_4$                  | 167.7  |
| Ether (Ethyl Oxide)                  | $(C_2H_5)_2O$                     | 302.09 |
| Ethyl Acetate                        | $C_2H_5C_2H_3O_2$                 | 74.08  |
| " Carbamate                          | $CO(OC_2H_5)NH_2$                 | 88.06  |
| " Chloride                           | $C_2H_5Cl$                        | 89.07  |
| " Hydroxide (Ethyl Alcohol)          | $C_2H_5OH$                        | 64.50  |
| Ethylmorphine Hydrochloride          | $C_{19}H_{23}O_3NHCl + 2H_2O$     | 46.05  |
| " Anhydrous                          | $C_{19}H_{23}O_3NHCl$             | 385.69 |
| Ethyl Nitrite                        | $C_2H_5NO_2$                      | 349.66 |
| " Oxide (Etuor)                      | $(C_2H_5)_2O$                     | 75.05  |
| Eucaine (Beta)                       | $C_{15}H_{21}O_2NHCl + H_2O$      | 74.08  |
| Eucalyptol (Cineol)                  | $C_{10}H_{18}O$                   | 301.66 |
| Eugenol                              | $C_{10}H_{12}O_2$                 | 154.14 |
| <b>Europium</b>                      | <b>Eu</b>                         | 164.10 |
| Ferric Acetate                       | $Fe(C_2H_3O_2)_3$                 | 152.0  |
| " Ammonium Sulphate                  | $FeNH_4(SO_4)_2 + 12H_2O$         | 232.91 |
| " " Anhydrous                        | $FeNH_4(SO_4)_2$                  | 482.21 |
| " Chloride                           | $FeCl_3 + 6H_2O$                  | 266.02 |
| " " Anhydrous                        | $FeCl_3$                          | 270.32 |
| " Hydroxide                          | $Fe(OH)_3$                        | 162.22 |
| " Hypophosphite                      | $Fe(PH_2O_2)_3$                   | 106.86 |
| " Nitrate                            | $Fe(NO_3)_3$                      | 251.01 |
| " Oxide                              | $Fe_2O_3$                         | 241.87 |
| " Phosphate (normal, not U.S.P.)     | $FePO_4$                          | 159.68 |
| " Pyrophosphate (normal, not U.S.P.) | $Fe_2(P_2O_7)_3$                  | 150.88 |
| " Subsulphate (variable)             |                                   | 745.60 |
| " Sulphate (Tersulphate)             | $Fe_2(SO_4)_3$                    |        |
| Ferrous Bromide                      | $FeBr_2 + 6H_2O$                  | 399.89 |
| " " Anhydrous                        | $FeBr_2$                          | 323.78 |
| " Carbonate                          | $FeCO_3$                          | 215.68 |
| " Iodide                             | $FeI_2$                           | 115.84 |
| " Lactate                            | $Fe(C_3H_5O_3)_2 + 3H_2O$         | 309.68 |
| " " Anhydrous                        | $Fe(C_3H_5O_3)_2$                 | 287.97 |
| " Oxide                              | $FeO$                             | 233.92 |
| " Sulphate                           | $FeSO_4 + 7H_2O$                  | 71.84  |
| " " Anhydrous                        | $FeSO_4$                          | 278.02 |
| " " Exsiccated (approximately)       | $2FeSO_4 + 3H_2O$                 | 151.91 |
| " Sulphide                           | $FeS$                             | 357.87 |
| <b>Ferrum</b>                        | <b>Fe</b>                         | 87.91  |
| Fluorescein (Resorcinolphthalein)    | $C_{20}H_{12}O_5$                 | 55.84  |
| <b>Fluorine</b>                      | <b>F</b>                          | 332.10 |
|                                      |                                   | 19.0   |

Practically nontoxic. A mild local irritant. Large doses orally can cause diarrhea.

**VET USE:** Locally as styptic. Diluted orally in G.I. tract hemorrhages.

**Ferric Sulfate.** Ferric persulfate; ferric sesquisulfate; ferric tersulfate,  $\text{Fe}_2(\text{SO}_4)_3$ ; mol wt 399.88. Fe 27.93%, O 48.01%, S 24.06%. Prepn: *Gmelin's Handb. anorg. Chem.*, System no. 59 (Iron), part B, pp 439-462 (1932).

Grayish-white powder, or rhombic or rhombohedral crystals. Very hygroscopic. Commercial product usually contains about 20% water and is yellowish in color.  $d_{4}^{20}$  3.097. Slowly sol in water, rapidly sol in the presence of a trace of  $\text{FeSO}_4$ ; sparingly sol in alcohol; practically insol in acetone, ethyl acetate. Hydrolyzed slowly in aq soln. *Keep well closed and protected from light.* LD s.c. in frogs: 13 g/kg.

**USE:** In prepn of iron alums, other iron salts and pigments; as coagulant in water purification and sewage treatment; in etching aluminum; in pickling stainless steel and copper; as mordant in textile dyeing and calico printing; in soil conditioners; as polymerization catalyst.

**Ferric Tannate.** Ferric gallotannate. Variable composition. Contains 8-10% Fe, 70-80% tannin.

Bluish-black powder. Insoluble in water; sol in dil mineral acids.

**USE:** In inks.

**Ferric Thiocyanate.** Ferric sulfocyanate; ferric sulfocyanide,  $\text{Fe}(\text{SCN})_3$ ; mol wt 230.08.  $\text{C}_3\text{FeN}_3\text{S}_3$ ; C 15.66%, Fe 24.27%, N 18.26%, S 41.81%. Prepn: *Gmelin's Handb. anorg. Chem.*, System no. 59 (Iron), part B, pp 747-761 (1932); Uri, *J. Chem. Soc.* 1947, 336.

Sesquihydrate,  $\text{Fe}(\text{SCN})_3 \cdot 1\frac{1}{2}\text{H}_2\text{O}$ , red, deliquescent crystals. Dec on heating. Soluble in water, alcohol, ether, acetone, pyridine, ethyl acetate; practically insol in  $\text{CHCl}_3$ ,  $\text{CCl}_4$ ,  $\text{CS}_2$ , toluene. *Keep well closed.*

**USE:** Analytical reagent.

**Ferrite.** Ferrosphenel. A crystalline, usually man-made material, having a spinel structure and consisting essentially of ferric oxide and at least one other metallic oxide which is usually, although not always, divalent in nature. When molded into compressed bodies, the material is characterized by high magnetic permeability. Typical composition:  $\text{Fe}_2\text{O}_3$  67-70%;  $\text{ZnO}$  10-10.5%;  $\text{MnO}_2$  20-22.5%;  $\text{CuO}$  0.1-10%;  $\text{Co}_3\text{O}_4$  0.1%. Ferrites are prepd by ceramic techniques. The oxides or carbonates are milled in steel ball mills, and the mixture of very fine particles is dried and pre-fired in order to obtain a homogeneous end product: Hilpert, *Ber.* 42, 2248 (1909). Examples of modern techniques: Simpkins, U.S. pat. 2,723,238 (1955 to Radio Corp. of America); Harvey, U.S. pat. 2,723,239 (1955 to Radio Corp. of America). Books: Snoek, *New Developments in Ferromagnetic Materials* (Elsevier, New York, 1947); Smit, Wijn, *Ferrites* (John Wiley & Sons, Inc., New York, 1959); Soohov, *Theory and Application of Ferrites* (Prentice Hall, 1960); Standley, *Oxide Magnetic Materials* (Clarendon Press, Oxford, 1962). *Reviews with bibliographies:* Gorter, *Proc. I.R.E.* 43, 1945-1973 (1955); Fresh, "Methods of Preparation and Crystal Chemistry of Ferrites," *ibid.* 44, 1303-1311 (1956); Brailsford, *Magnetic Materials* (3rd ed, John Wiley & Sons, Inc., 1960), pp 160-181; Hogan, *Sci. Am.* 202, 92-104 (1960); Economos, Kirk-Othmer's *Encyclopedia of Chemical Technology* vol. 8 (2nd ed, Interscience, 1965), pp 881-901.

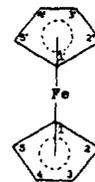
**USE:** Radio and television coil cores; slug tuners, loop-stick antennas. **Human Toxicity:** The dust can cause pulmonary irritation. *See also specific metals.*

**Ferritin.** A crystallizable protein contg 20-24% iron and 1.2-2% phosphorus. Forms a large part of the storage iron in spleen, intestinal mucosa, and liver. Isolated from horse spleen. *Review:* Kleinwachter, *Chem. Listy* 55, 234 (1961).

**Ferroakermanite.**  $2\text{CaO} \cdot \text{FeO} \cdot 2\text{SiO}_2$ —calcium iron silicate.

**Ferrocene.** *Dicyclopentadienyliron*; biscyclopentadienyliron.  $\text{C}_{10}\text{H}_{10}\text{Fe}$ ; mol wt 186.03. C 64.56%, H 5.42%, Fe 30.02%. Preps: Kealy and Pauson, *Nature* 168, 1039 (1951); Pauson, U.S. pat. 2,680,756 (1954 to Du Pont); Miller et al., *J. Chem. Soc.* 1952, 632; Anzilotti and Weinmayr, U.S. pat. 2,791,597 (1957 to Du Pont). Other preps: Wilkinson, *Org. Syn.* 36, 31, 34 (1956); Pruett, Morehouse, *Advances in Chemistry Series* 23, 368-371 (1959); Wilkinson, *Org. Syn.*, coll. vol. IV, 473 (1963); Cordes, *Fr. pat.* 1,341,880

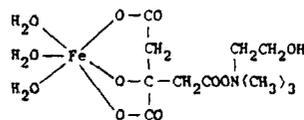
(1963 to BASF); C.A. 60, 6873a. Structure studies: Wilkinson et al., *J. Am. Chem. Soc.* 74, 2125 (1952); Seibold and Sutton, *J. Chem. Phys.* 23, 1967 (1955). *Review on ferrocene reactions:* Rausch et al., *J. Chem. Ed.* 34, 268 (1957). Book: Rosenblum, *Chemistry of the Iron Group Metalloenes* (John Wiley, New York), 1965.



Orange needles from methanol or ethanol; odor of camphor. mp 173-174°. Sublimes above 100°. Volatile in steam. Practically insol in water, 10% NaOH, and concd boiling HCl. Soluble in alcohol, ether, benzene. Also dissolves in dil nitric and concd sulfuric acids forming a deep red soln with blue fluorescence. The molecule is diamagnetic and the dipole moment is effectively zero.

**USE:** Antiknock additive for gasoline; catalyst. **Human Toxicity:** No specific data. Animal feeding expts show almost complete absence of toxicity.

**Ferrocinate.** [*Hydrogen citrato(3-)*]triquiron, choline salt; iron choline citrate; Chelafer; Chel-Iron; Ferrilip.  $\text{C}_{11}\text{H}_{24}\text{FeNO}_{11}$ ; mol wt 402.17. C 32.85%, H 6.01%, Fe 13.89%, N 3.48%, O 43.76%. Prepd by interaction of equimolar quantities of choline dihydrogen citrate and freshly prepd  $\text{Fe}(\text{OH})_3$  or  $\text{FeCO}_3$ : Bandelin, U.S. pat. 2,575,611 (1951 to Flint Eaton & Co.); by treatment of a freshly prepd soln of ferric citrate with an equimolar amount of choline: Chakrabarti, Sen, *Chemistry & Industry (London)* 1961, 1407.



Greenish-brown, reddish-brown or brown amorphous solid with glistening surface upon fracture. Freely sol in water, yielding stable solns; sol in acids, alkalis. One gram of pharmaceutical grade is equivalent to 120 mg of elemental iron and 360 mg of choline base.

**Note:** Other combinations of iron, choline and citric acid have been prepd for pharmaceutical use. A 1:2:2 chelate,  $\text{C}_{22}\text{H}_{36}\text{FeN}_2\text{O}_{16}$ , was reported by Chakrabarti and Sen, *loc. cit.*, and a 2:3:3 chelate,  $\text{C}_{33}\text{H}_{57}\text{Fe}_2\text{N}_3\text{O}_{24}$ , by Rosenfelder, U.S. pat. 2,865,938 (1958 to H. Rosenstein).

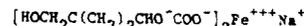
**MED USE:** Hematinic in iron deficiency anemia.

**Ferrodolomite.**  $\text{CaFe}(\text{CO}_3)_2$ —calcium iron carbonate.

**Ferroglycine Sulfate.** Ferroglycine sulfate complex; ferrous sulfate glycine complex; ferrous aminoacetosulfate; iron sulfate-glycine complex; glycine-ferrous sulfate complex; Plesmet; Kelferon; Ferronord; Glyferro; Pleniron. Prepn from glycine and ferrous sulfate: Rummel, U.S. pats. 2,877,253 and 2,957,806 (1959 and 1960 to Dr. Schwarz Arzneimittel-fabrik GmbH).

**MED USE:** In iron deficiency anemia. **Dose:** Oral 1-2 tablets (40-80 mg of ferrous iron). **Side Effects:** G.I. disturbances may occur. *See also Ferrous Sulfate.*

**Ferronascin.** 2,4-Dihydroxy-3,3-dimethylbutyric acid iron derivative sodium salt; bis( $\alpha,\gamma$ -dihydroxy- $\beta,\beta$ -dimethylbutyrate)ferric acid sodium salt; sodium bis( $\alpha,\gamma$ -dihydroxy- $\beta,\beta$ -dimethylbutyryl)ferrate.  $\text{C}_{12}\text{H}_{20}\text{FeNaO}_8$ ; mol wt 371.13. C 38.84%, H 5.43%, Fe 15.05%, Na 6.19%, O 34.49%. Prepn: Schneider, U.S. pat. 2,474,989 (1949 to Hoffmann-La Roche).



Brown soln of yellowish-brown solid. The free acid is precipitated from acetone as a pale yellow-brown powder, becoming brown on heating above 150°.

**MED USE:** Hematinic for iron deficiency anemia. **Dose:** i.v. 2 ml (= 20 mg of iron). **Side Effects:** Thrombosis of the injected vein, headache, flushing, G.I. symptoms may occur.

*Consult the cross index before using this section*

vol 2, G. Brauer, Ed. (Academic Press, d., 1965) p 1499. Crystal structure of anion, *Acta Cryst.* 25B, 1683 (1969). Review: *M. Bull.* 4, 15-30 (1959).

or crystals. Loses H<sub>2</sub>O to form ally insol in water, alcohol. Sol in

ig water; as absorbent in chemical process is catalyst.

**c Hypophosphate.** FeH<sub>2</sub>O<sub>2</sub>P<sub>3</sub>; mol wt 7%. H 2.41%, O 38.27%, P 37.05%. Fe. U.S.D. 25th ed. p 573.

sh-white powder. Odorless, tasteless. Sol in water, 1200 parts boiling water; more sol of H<sub>2</sub>PO<sub>2</sub>; sol in warm concd solns of *roset* from light. Should not be heated or chlorates, nitrates, or other oxidizing agents. as dietary supplement for phosphorus.

**late Calcium Sodium. Pentaqua[*D*-gluco-*D*]tetra-*n*-hydroxydioxotri ferrate(3-) cal-1:4); monocalcium tetrasodium bis(penta-oxo[*D*-gluconato(4-)]dioxotri ferrate(3-)); (Fe<sub>2</sub>Na<sub>4</sub>O<sub>3</sub>); mol wt 1231.57. C 11.70%, H Fe 27.21%, Na 7.47%, O 46.77%. Hematinic.**

**Nitrate.** Fe<sub>2</sub>N<sub>3</sub>O<sub>3</sub>; mol wt 241.86. Fe %, O 59.54%. Fe(NO<sub>3</sub>)<sub>3</sub>. Prepn: *Gmelin's*, part B, 161-172 (1932). Toxicity study: *Am. Ind. Hyg. Assoc. J.* 30, 470 (1969). pale-violet to grayish-white, somewhat delinq 47°. Dec below 100°. d<sub>4</sub><sup>20</sup> 1.68. Freely sol in water, acetone; slightly sol in cold concd ally in rats: 3.25 g/kg (Smyth). ant in dyeing, weighting silks, tanning; as ical chemistry; as corrosion inhibitor.

**c Oxide.** Ferric sesquioxide; jeweler's sol wt 159.69. Fe 69.94%, O 30.06%. a- nature as the mineral *hematite*.  $\gamma$ -Form oc- the mineral *maghemite*; prepd by dehydra- (H): Giovanoli, Brütisch, *Chimia* 28, 188 a th<sub>2</sub> allomorphic form,  $\epsilon$ -Fe<sub>2</sub>O<sub>3</sub>; Schra- *Allgem. Chem.* 320, 220 (1963); st. *pt. Rend.* 261, 4423 (1965). Col- of Fe<sub>2</sub>O<sub>3</sub> are dependent upon the size and ticles and the amount of combined water. properties: *Gmelin's, Iron* (8th ed.) 59, part 3; Baudisch, Hartung, *Inorg. Syn.* 1, 185 *s Encyklopädie der Technischen Chemie* vol. 5); Bernal *et al.*, *Clay Miner. Bull.* 4, 15-30 ogy: L. T. Fairhall, *Industrial Toxicology* ork, 2nd ed., 1969) pp 64-66. nposition of the substance called  $\delta$ -Fe<sub>2</sub>O<sub>3</sub> is 1) (Bernal *et al.*).

ntial symptoms of overexposure to dust and i pneumoconiosis with x-ray shadows indism fibrotic pneumoconiosis. See *NIOSH Chemical Hazards* (DHHS/NIOSH 90-117, rhall, *loc. cit.* ant for rubber, paints, paper, linoleum, cera- nant for ironwork, ship hulls; as polishing precious metals, diamonds; in electrical r-conductors; in magnets, magnetic tapes; as ul solns as stain for polysaccharides.

**c Oxide, Saccharated.** Saccharated iron; iliron I.V.; Feojectin; Ferrivenin; Ferum on; Neo-Ferrum; Proferrin; Suferfer. Con- ce. Prepn: U.S.D. 26th ed., p 627 (1967). mtg 2% Fe suitable for i.v. injection: Slack, *er* 256, 11 (1949). r. Sol in water. Practically insol in alcohol. ble in the presence of electrolytes: *Do not ogical saline!* Hematinic.

**c Phosphate.** FeO<sub>4</sub>P; mol wt 150.82. Fe 3%, P 20.54%. FePO<sub>4</sub>. Occurs in nature as *beraunite*, *cacoxenite*, *dufrenite*, *koninckite*,

*phosphosiderite*, *strengite*. Prepn from Fe(H<sub>2</sub>PO<sub>4</sub>)<sub>3</sub>; Remy, *Boullé, Compt. Rend.* 253, 2699 (1961); from Fe(CO)<sub>5</sub> and H<sub>2</sub>PO<sub>4</sub>; Cate *et al.*, *Soil Sci.* 88(3), 130 (1959); from phosphate rock: Vickery, U.S. pat. 2,914,380 (1959 to Horizons Inc.); from mill scale and H<sub>2</sub>PO<sub>4</sub>; Alexander, Mathes, U.S. pat. 3,070,423 (1962 to Chemetron).

Dihydrate, white, grayish-white, or light pink, ortho- rhombic or monoclinic crystals or amorphous powder. Loses water above 140°. d 2.87. Practically insol in water. Slowly sol in HNO<sub>3</sub>; readily sol in HCl.

USE: As food and feed supplement, particularly in bread enrichment; as fertilizer.

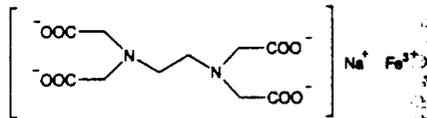
**4075. Ferric Pyrophosphate.** Fe<sub>2</sub>O<sub>2</sub>P<sub>2</sub>; mol wt 745.21. Fe 29.98%, O 45.09%, P 24.94%. Fe<sub>2</sub>(P<sub>2</sub>O<sub>7</sub>)<sub>3</sub>. Prepn: *Gmelin's, Iron* (8th ed.) 59, part B, 777 (1932); Knight, Kelly, U.S. pat. 3,014,784 (1962 to American Oil).

Nonahydrate, yellowish-white powder. Practically insol in water or acetic acid. Sol in mineral acids.

USE: As catalyst; in fireproofing of synthetic fibers; in corrosion-preventing pigments.

THERAP CAT: Hematinic.

**4076. Ferric Sodium Edetate.** [(N,N'-Ethanediylbis[*N*-(carboxymethyl)glycinato]](4-)-N,N',O,O',O',O'-ferrate(1-)-sodium; sodium [(ethylenedinitrilo)tetraacetato]ferrate(1-); (ethylenedinitrilo)tetraacetic acid sodium salt iron complex; ferric monosodium ethylenediaminetetraacetate; edetic acid sodium iron salt; sodium iron edetate; sodium feredetate; Ferrostrane; Ferrostrene; Sybron. C<sub>10</sub>H<sub>16</sub>FeN<sub>2</sub>NaO<sub>8</sub>; mol wt 367.05. C 32.72%, H 3.30%, Fe 15.21%, N 7.63%, Na 6.26%, O 34.87%. Prepd from disodium ethylenediaminetetraacetic acid and ferric nitrate: Sawyer, McKinnic, *J. Am. Chem. Soc.* 82, 4191 (1960).



Crystals from water + ethanol. THERAP CAT: Iron source.

**4077. Ferric Sodium Pyrophosphate.** Sodium ferric pyrophosphate. Fe<sub>2</sub>Na<sub>2</sub>O<sub>7</sub>P<sub>2</sub>; mol wt 1277.02. Fe 17.49%, Na 14.40%, O 43.85%, P 24.25%. Hydrate: Fe<sub>2</sub>(P<sub>2</sub>O<sub>7</sub>)<sub>2</sub>.xH<sub>2</sub>O. The commercial product contains 15.5% 16.5% Fe and 50.5-52.5% P<sub>2</sub>O<sub>5</sub>.

White powder. Bulk density 1.4-1.6. Sol in hydrochloric acid. Insol in water.

USE: Food enrichment. Less prone to induce rancidity than orthophosphates.

**4078. Ferric Sub sulfate Solution.** Basic ferric sulfate soln; Monsel's soln. Approx: Fe<sub>2</sub>(OH)(SO<sub>4</sub>)<sub>3</sub>. Prepn from FeSO<sub>4</sub> and HNO<sub>3</sub>; U.S.D. 25th ed., p 574.

Reddish-brown liquid. Almost odorless; sour, strongly astringent taste. Acid to litmus. Affected by light. d<sub>4</sub><sup>20</sup> 1.548. Miscible with water, alcohol. May crystallize and solidify at low temps. *Keep well closed, protected from light in a warm place.*

USE: As mordant in dyeing textiles. THERAP CAT: Styptic.

THERAP CAT (VET): Styptic, astringent.

**4079. Ferric Sulfate.** Ferric persulfate; ferric sulfate; ferric tersulfate. Fe<sub>2</sub>O<sub>12</sub>S<sub>3</sub>; mol wt 399.88. Fe 27.93%, O 48.01%, S 24.06%. Fe<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub>. Prepn: *Gmelin's, Iron* (8th ed.) 59, part B, 439-462 (1932).

Grayish-white powder, or rhombic or rhombohedral crystals. Very hygroscopic. Commercial product usually contains about 20% water and is yellowish in color. d<sub>4</sub><sup>20</sup> 1.57. Slowly sol in water, rapidly sol in the presence of a trace of FeSO<sub>4</sub>; sparingly sol in alcohol; practically insol in acetic acid, ethyl acetate. Hydrolyzed slowly in aq soln. *Keep well closed and protected from light.*

USE: In preparation of iron alums, other iron salt pigments; as coagulant in water purification and in treatment; in etching aluminum; in pickling stainless

and copper; as mordant in textile dyeing and calico printing; in soil conditioners; as polymerization catalyst.

**4080. Ferric Tannate.** Ferric gallotannate. Variable composition. Contains 8-10% Fe, 70-80% tannin.

Bluish-black powder. Insol in water; sol in dil mineral acids. USE: In inks.

**4081. Ferric Thiocyanate.** Ferric sulfocyanate; ferric sulfocyanide. C<sub>2</sub>FeN<sub>2</sub>S<sub>3</sub>; mol wt 230.10. C 15.66%, Fe 24.27%, N 18.26%, S 41.81%. Fe(SCN)<sub>3</sub>. Prepn: *Gmelin's Handb. Anorg. Chem., Iron* (8th ed.) part B, 747-761 (1932). Sesquihydrate, red, deliquescent crystals. Dec on heating. Sol in water, alcohol, ether, acetone, pyridine, ethyl acetate. Practically insol in CHCl<sub>3</sub>, CCl<sub>4</sub>, CS<sub>2</sub>, toluene. *Keep well closed.*

USE: Analytical reagent.

**4082. Ferrite.** Ferrosipinel. A crystalline, usually man-made material, having a spinel structure and consisting essentially of ferric oxide and at least one other metallic oxide which is usually, although not always, divalent in nature. When molded into compressed bodies, the material is characterized by high magnetic permeability. Typical composition: Fe<sub>2</sub>O<sub>3</sub> 67-70%; ZnO 10-10.5%; MnO<sub>2</sub> 20-22.5%; CuO 0.1-10%; Co<sub>2</sub>O<sub>3</sub> 0.1%. Ferrites are prepd by ceramic techniques. The oxides or carbonates are milled in steel ball mills, and the mixture of very fine particles is dried and pre-fired in order to obtain a homogeneous end product: Hilpert, *Ber.* 42, 2248 (1909). Examples of modern techniques: Simpkins; Harvey, U.S. pats 2,723,238-9 (both 1955 to RCA). Prepn of single crystals: Rooymans, *Colloq. Int. Cent. Nat. Rech. Sci.* No. 205, 151 (1972). Books: Snoeck, *New Developments in Ferromagnetic Materials* (Elsevier, New York, 1947); Smit, Wijn, *Ferrites* (John Wiley, New York, 1959); Soohov, *Theory and Applications of Ferrites* (Prentice Hall, 1960); Standley, *Oxide Magnetic Materials* (Clarendon Press, Oxford, 1962); *Ferrites, Proc. Int. Conf.*, Y. Hoshino *et al.*, Eds. (University Park Press, Baltimore, 1971) 671 pp; E. E. Riches, *Ferrites, A Review of Materials and Applications* (Mills and Boon, London, 1972) 88 pp. Reviews with bibliographies: Gorter, *Proc. I.R.E.* 43, 1945-1973 (1955); Fresh, "Methods of Preparation and Crystal Chemistry of Ferrites," *ibid.* 44, 1303-1311 (1956); Brailsford, *Magnetic Materials* (John Wiley, New York, 3rd ed., 1960) pp 160-181; Hogen, *Sci. Am.* 202, 92-104 (1960); Economos in Kirk-Othmer's *Encyclopedia of Chemical Technology* vol. 8 (Interscience, New York, 2nd ed., 1965) pp 881-901; Gray, "Oxide Spinel" in *High Temperature Oxides*, Part IV, A. M. Alper, Ed. (Academic Press, New York, 1971) pp 77-107.

Note: The term "ferrites" has been expanded to mean any oxidic magnetic material.

USE: Magnetic cores for inductors and transformers; microwave devices; information storage; electromechanical transducers: E. E. Riches, *loc. cit.*; Brockman, *Ceram. Ind.* 99, 24 (1972).

**4083. Ferritin.** Epadora; Ferrofolin; Ferrrol; Ferro-sprint; Ferrostar; Sanifer; Sideros; Unifer. Major iron storage protein; found in spleen, liver and intestinal mucosa of vertebrates; widely distributed in the plant and animal kingdoms. Insol and crystallization of horse spleen ferritin: Lauffer, *Bull. Soc. Chim. Biol.* 19, 1575 (1937); Granick, *J. Biol. Chem.* 14, 451 (1942); Crichton *et al.*, *Biochem. J.* 131, 51 (1973). Consists of a protein shell surrounding a crystalline, hydrated iron oxide/phosphate core. The core may contain up to 4500 Fe<sup>3+</sup> ions; unfractionated, horse-spleen ferritin contains approx 20% iron on a dry weight basis. The protein shell, *apoferritin*, has a mol wt of ~445,000. Several proposed structures of protein moiety: Harrison, *J. Mol. Biol.* 6, 404 (1963); Crichton, *Biochem. J.* 126, 761 (1972); Niitsu *et al.*, *Biochem. Biophys. Res. Commun.* 55, 1134 (1973). Absorption spectra: Granick, *Chem. Rev.* 38, 379 (1946). Use of serum ferritin and isoferritins in clinical medicine: J. W. Halliday, L. W. Powell, *Prog. Hematol.* 11, 229 (1979). Reviews: Harrison, H., "Ferritin" in *Inorganic Biochemistry* vol. 1, G. L. Eichhorn, Ed. (Elsevier, New York, 1973) pp 253-277; Crichton, *Angew.*

Database: Medline <1966 to present>

<1>

Unique Identifier

97406844

Authors

Fuks AB. Holan G. Davis JM. Eidelman E.

Title

- Ferric sulfate versus dilute formocresol in pulpotomized primary molars: long-term follow up.

Source

Pediatric Dentistry. 19(5):327-30, 1997 Jul-Aug.

Abstract

H  
The aim of this study was to compare the effect of ferric sulfate (FS) to that of dilute formocresol (DFC) as pulp dressing agents in pulpotomized primary molars. Ninety-six primary molars in 72 children were treated by a conventional pulpotomy technique. Fifty-eight teeth were treated by a FS solution for 15 sec, rinsed, and covered by zinc oxide-eugenol paste (ZOE). In another 38 teeth, a cotton pellet moistened with 20% DFC was placed for 5 min, removed, and the pulp stumps were covered by ZOE paste. The teeth of both groups were sealed by a second layer of intermediate restorative material (IRM) and restored with a stainless steel crown. This is a report of the clinical and radiographic examination of 55 teeth dressed with FS and 37 teeth fixed with DFC, that have been treated 6 to 34 months previously (mean 20.5 months). Four teeth were excluded from the study due to failure of the patient to present for recall. Success rates of 92.7% for the FS, and of 83.8% for the DFC were not significantly different. Four teeth (7.2%) of the FS group and two (5.4%) of the DFC group presented internal resorption. Inter-radicular radiolucencies were observed in two teeth of the FS group and three teeth of the DFC group. The latter also presented periapical lesions. Success rates of both groups were similar to those of previous studies utilizing the traditional Buckley's formocresol.

<2>

Unique Identifier

97391944

Authors

Kim S. Rethnam S.

Title

Hemostasis in endodontic microsurgery.

Unique Identifier

93316024

Authors

Jeansonne BG. Boggs WS. Lemon RR.

Title

Ferric sulfate hemostasis: effect on osseous wound healing.  
II. With curettage and irrigation.

Source

Journal of Endodontics. 19(4):174-6, 1993 Apr.

Abstract

Hemorrhage control is often a problem for the clinician during osseous surgery. Ferric sulfate is an effective hemostatic agent, but with prolonged application to an osseous defect can cause persistent inflammation and delayed healing. The purpose of this investigation was to evaluate the effectiveness of ferric sulfate as a hemostatic agent and to determine its effect on healing after thorough curettage and irrigation from osseous surgical wounds. Standard size osseous defects were created bilaterally in the mandibles of rabbits. Ferric sulfate was placed in one defect until hemostasis was obtained; the contralateral defect was allowed to fill with blood and clot. After 5 min both defects were curetted and irrigated. The repair of the defects was evaluated histologically at 18 and 46 days. There were no significant differences between the ferric sulfate-treated defects and the untreated controls. When adequately curetted and irrigated from the surgical site prior to closure, ferric sulfate did not cause persistent inflammation or delay osseous repair in comparison to controls.

<6>

Unique Identifier

93316023

Authors

Lemon RR. Steele PJ. Jeansonne BG.

Title

Ferric sulfate hemostasis: effect on osseous wound healing.  
Left in situ for maximum exposure.

Source

Journal of Endodontics. 19(4):170-3, 1993 Apr.

Abstract

Ferric sulfate solution is an accepted soft tissue hemostatic agent for use in dermatology and dentistry. This study was designed to test its effect on osseous healing when used during surgery to control osseous hemorrhage. Standardized osseous defects were created bilaterally in the naturally edentulous zone in rabbit mandibles. The

control site was sutured immediately after clot formation in the defect. The contralateral experimental site received ferric sulfate application until complete hemostasis was achieved. The defect was filled with ferric sulfate solution to maximize any effect on healing and then closed with sutures. The experimental and control specimens were examined histologically after 18 and 46 days and scored for healing. Statistical analysis by Wilcoxon signed rank test showed significant adverse effects on osseous healing when ferric sulfate solution was left in situ.

<7>

Unique Identifier

93181319

Authors

Fei AL. Udin RD. Johnson R.

Title

A clinical study of ferric sulfate as a pulpotomy agent in primary teeth.

Source

Pediatric Dentistry. 13(6):327-32, 1991 Nov-Dec.

Abstract

Pulpotomies were performed on 83 primary molars in 62 patients. Ferric sulfate or formocresol was placed on the pulpal stumps, and teeth were followed for 3-, 6-, and 12-month periods. After the one-year follow-up, 28 of 29 teeth treated with ferric sulfate (FS group) were considered successful and 21 of 27 teeth treated with formocresol (FC group) were judged to be successful. The FS group demonstrated greater combined clinical and radiographic success than the FC group at the one-year recall ( $P < 0.05$ ). Although the results of this study are promising, further study with longer observation periods is warranted before this technique can be recommended.

## Source

Dental Clinics of North America. 41(3):499-511, 1997 Jul.  
Abstract

There are numerous ways to achieve hemostasis. With the abundance of hemostatic agents available and with the introduction of new products, one has to make an objective decision. A good agent achieves hemostasis within a short period of time, is easy to manipulate, is biocompatible, does not impair or retard healing, must be relatively inexpensive, is reliable, and works best for the particular surgical procedure. With these purposes in mind, the following sequence is recommended to achieve hemostasis during endodontic microsurgery. I. Presurgical: Give 2 to 3 Carpules of 1:50,000 epinephrine local anesthetic with multiple infiltration sites throughout the entire surgical field. II. Surgical: A. Remove all granulation tissue. B. Place an epinephrine pellet into the bony crypt followed by dry sterile cotton pellets. Apply pressure for 2 minutes. Remove all the cotton pellets except the first epinephrine pellet. Continue with the surgical procedure and remove the epinephrine pellet before final irrigation and closure. C. Alternatively, calcium sulfate can be mixed into a thick putty and packed against the bone cavity. Because it is a biodegradable material, calcium sulfate can be left in situ. In fact, in large bone defects and through-and-through lesions, additional calcium sulfate can be placed to fill the entire bone cavity as a barrier material. Healing is more predictable with little chance of scar tissue formation. Calcium sulfate resorbs in 2 to 4 weeks. D. Small bleeding sites in the bone can be brushed with ferric sulfate solution. III. Postsurgical: Tissue compression before and after suturing cuts down on postsurgical bleeding and swelling. Hemostasis is imperative in endodontic microsurgery for better visualization, a good environment for placement of retrograde filling material, and a more efficient surgical procedure with less blood loss.

<3>

Unique Identifier

84144452

Authors

Shaw DH. Krejci RF. Kalkwarf KL. Wentz FM.

Title

Gingival response to retraction by ferric sulfate (Astringent).

Source

Operative Dentistry. 8(4):142-7, 1983 Autumn.

**A. INGREDIENT NAME:**

**GUAIACOL**

**B. Chemical Name:**

Guajacol, Guaiacol, Guaicoo, Guajakol (CZECH), O-Hydroxyanisole, 2-Hydroxyanisole, 1-Hydroxy-2-Methoxybenzene, O-Methoxyphenol, 2-Methoxyphenol, Methylcatechol, Pyroguaiac Acid

**C. Common Name:**

Austral: Waterbury's Compound, Belg: Baume Dalet, Canada: Cre-Rectal, etc. Various names from different countries. Please see file.

**D. Chemical grade or description of the strength, quality, and purity of the ingredient:**

|        | <i>(Specifications)</i> | <i>(Results)</i> |
|--------|-------------------------|------------------|
| Assay: | 99.5% min.              | 99.7%            |

**E. Information about how the ingredient is supplied:**

White or slightly yellow crystal mass or colorless to yellowish, very refractive liquid, characteristic odor, darkens to exposure to air and light.

**F. Information about recognition of the substance in foreign pharmacopeias:**

Arg., Braz., Chil., Fr., It., Mex., Port., Roum., Span., and Swiss.

**G. Bibliography of available safety and efficacy data including peer reviewed medical literature:**

**H. Information about dosage forms used:**

Expectorant

**I. Information about strength:**

0.3-0.6ml

**J. Information about route of administration:**

Orally

**K. Stability data:**

Boiling Point: 205C

Melting Point: 27C to 29C

**L. Formulations:**

**M. Miscellaneous Information:**

CERTIFICATE OF ANALYSIS

30-1709  
# 50703

PRODUCT: GUAIACOL LIQUID  
RELEASE #: N

LOT # :X49993D28

GRADE: PURIFIED  
CODE: R9128201

SPECIFICATIONS

RESULT

|                         |   |  |
|-------------------------|---|--|
| 1. Description          | Colorless liquid ,<br>characteristic odor | Conforms                                   |
| 2. Solidification point | 27.5 deg C min.                           | 28.0 deg C                                 |
| 3. Assay                | 99.5% min.                                | 99.7% <span style="float: right;">D</span> |

---

ATTENTION: TONY HATCHETT

Date :06/06/97

Prepared by : A.M. Scullion

9257

Approved by :  6/97

Our Order # 234202 Your PO # 52409

# QUALITY CONTROL REPORT

CHEMICAL NAME.: GUAIACOL PURIFIED (LIQUID) \_\_\_\_\_

MANUFACTURE LOT NO.: X49993D28

## PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP \_\_\_/BP \_\_\_/MERCK \_\_\_/NF \_\_\_/MART. \_\_\_/CO. SPECS. \_\_\_.

### 1) DESCRIPTION.:

E { WHITE OR SLIGHTLY YELLOW CRYSTAL MASS OR COLORLESS TO YELLOWISH,  
VERY REFRACTIVE LIQUID; CHARACTERISTIC ODOR; DARKENS ON EXPOSURE TO  
AIR AND LIGHT.

### 2) SOLUBILITY.:

1gm DISSOLVES IN 60-70ml WATER, 1ml GLYCEROL; MISCIBLE WITH ALCOHOL,  
CHLOROFORM, ETHER, OILS, GLACIAL ACETIC ACID; SOLUBLE IN NAOH SOLUTION;  
WITH MODERATELY CONC KOH, IT FORMS A SPARINGLY SOLUBLE COMPOUND.

### 3) MELTING POINT.:

### 4) SPECIFIC GRAVITY.:

### 5) IDENTIFICATION.:

A) COMPLIES IR SPECTRUM AS PER COMPANY SPECS.

PASSES.: \_\_\_\_\_

FAILS.: \_\_\_\_\_

COMMENTS.:

ANALYST SIGNATURE.: \_\_\_\_\_

DATE.: \_\_\_\_\_

PREPACK TEST.: \_\_\_\_\_

DATE.: \_\_\_\_\_

INITIAL.: \_\_\_\_\_

RETEST.: \_\_\_\_\_

DATE.: \_\_\_\_\_

INITIAL.: \_\_\_\_\_



**Fisher Scientific**



Use your web browser's "Back" key to return to previous topic.

**MATERIAL SAFETY DATA SHEET**

**Guaiacol, 99+%**  
06742

\*\*\*\* SECTION 1 - CHEMICAL PRODUCT AND COMPANY IDENTIFICATION \*\*\*\*

MSDS Name: Guaiacol, 99+%



2-Methoxyphenol

Company Identification: Acros Organics N.V.  
One Reagent Lane  
Fairlawn, NJ 07410

For information in North America, call: 800-ACROS-01  
For emergencies in the US, call CHEMTREC: 800-424-9300  
For emergencies in the US, call CHEMTREC: 800-424-9300

\*\*\*\* SECTION 2 - COMPOSITION, INFORMATION ON INGREDIENTS \*\*\*\*

| CAS#    | Chemical Name | %   | EINECS#   |
|---------|---------------|-----|-----------|
| 90-05-1 | GUAIACOL      | 99+ | 201-964-7 |

Hazard Symbols: XN  
Risk Phrases: 22 36/38

\*\*\*\* SECTION 3 - HAZARDS IDENTIFICATION \*\*\*\*

EMERGENCY OVERVIEW

Appearance: clear slightly yellow. Flash Point: 82 deg C.  
Light sensitive. Air sensitive.  
Target Organs: Central nervous system, eyes, skin.

Potential Health Effects

- Eye:  
Causes eye irritation. Causes redness and pain.
- Skin:  
Causes severe skin irritation. May be absorbed through the skin.  
Causes redness and pain.
- Ingestion:  
Harmful if swallowed. May cause gastrointestinal irritation with nausea, vomiting and diarrhea.
- Inhalation:  
May cause respiratory tract irritation.
- Chronic:  
Not available.

\*\*\*\* SECTION 4 - FIRST AID MEASURES \*\*\*\*

Eyes:  
 Immediately flush eyes with plenty of water for at least 15 minutes, occasionally lifting the upper and lower lids. Get medical aid.

Skin:  
 Get medical aid. Flush skin with plenty of soap and water for at least 15 minutes while removing contaminated clothing and shoes.

Ingestion:  
 Get medical aid. Wash mouth out with water.

Inhalation:  
 Remove from exposure to fresh air immediately. If not breathing, give artificial respiration. If breathing is difficult, give oxygen.

Notes to Physician:  
 Treat symptomatically and supportively.

\*\*\*\* SECTION 5 - FIRE FIGHTING MEASURES \*\*\*\*

General Information:  
 As in any fire, wear a self-contained breathing apparatus in pressure-demand, MSHA/NIOSH (approved or equivalent), and full protective gear. Combustible Liquid.

Extinguishing Media:  
 In case of fire use water spray, dry chemical, carbon dioxide, or chemical foam.

Autoignition Temperature: 385 deg C ( 725.00 deg F)  
 Flash Point: 82 deg C ( 179.60 deg F)  
 NFPA Rating: Not published.  
 Explosion Limits, Lower: Not available.  
 Upper: Not available.

\*\*\*\* SECTION 6 - ACCIDENTAL RELEASE MEASURES \*\*\*\*

General Information: Use proper personal protective equipment as indicated in Section 8.

Spills/Leaks:  
 Absorb spill with inert material, (e.g., dry sand or earth), then place into a chemical waste container. Remove all sources of ignition. Use a spark-proof tool.

\*\*\*\* SECTION 7 - HANDLING and STORAGE \*\*\*\*

Handling:  
 Avoid breathing dust, vapor, mist, or gas. Avoid contact with skin and eyes. Use only in a chemical fume hood.

Storage:  
 Keep away from sources of ignition. Store in a cool, dry place. Do not store in direct sunlight. Store in a tightly closed container.

\*\*\*\* SECTION 8 - EXPOSURE CONTROLS, PERSONAL PROTECTION \*\*\*\*

Engineering Controls:  
 Use adequate ventilation to keep airborne concentrations low.

Exposure Limits

| Chemical Name | ACGIH       | NIOSH       | OSHA - Final PELs |
|---------------|-------------|-------------|-------------------|
| GUAIACOL      | none listed | none listed | none listed       |

OSHA Vacated PELs:  
 GUAIACOL:  
 No OSHA Vacated PELs are listed for this chemical.

Personal Protective Equipment

Eyes:  
 Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133.

Skin: Wear appropriate protective gloves to prevent skin exposure.

Clothing: Wear appropriate protective clothing to prevent skin exposure.

Respirators: Follow the OSHA respirator regulations found in 29CFR 1910.134. Always use a NIOSH-approved respirator when necessary.

## \*\*\*\* SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES \*\*\*\*

Physical State: Liquid  
Appearance: clear slightly yellow  
Odor: Aromatic odor  
pH: Not available.  
Vapor Pressure: 7 hPa @ 79 deg C  
Vapor Density: 4.3  
Evaporation Rate: Not available.  
Viscosity: Not available.  
Boiling Point: 205 deg C @ 760.00mm Hg  
Freezing/Melting Point: 27 - 29 deg C  
Decomposition Temperature: Not available.  
Solubility: 1.7 G/100ML WATER (15°C)  
Specific Gravity/Density: 1.1290g/cm3  
Molecular Formula: C7H8O2  
Molecular Weight: 124.14

## \*\*\*\* SECTION 10 - STABILITY AND REACTIVITY \*\*\*\*

Chemical Stability: Stable under normal temperatures and pressures.

Conditions to Avoid: Incompatible materials, light, exposure to air.

Incompatibilities with Other Materials: Strong oxidizing agents - strong bases - acid chlorides - acid anhydrides.

Hazardous Decomposition Products: Carbon monoxide, carbon dioxide.

Hazardous Polymerization: Will not occur.

## \*\*\*\* SECTION 11 - TOXICOLOGICAL INFORMATION \*\*\*\*

RTECS#:  
CAS# 90-05-1: SL7525000  
LD50/LC50:  
CAS# 90-05-1: Inhalation, mouse: LC50 = 7570 mg/m3; Oral, mouse: LD50 = 621 mg/kg; Oral, rat: LD50 = 520 mg/kg; Skin, rabbit: LD50 = 4600 mg/kg.

Carcinogenicity:  
GUAIACOL -  
Not listed by ACGIH, IARC, NIOSH, NTP, or OSHA.

## \*\*\*\* SECTION 12 - ECOLOGICAL INFORMATION \*\*\*\*

Ecotoxicity:  
EC 50 (24 hr) Daphnia magna: 63 mg/l

Environmental Fate:  
Guaiacol is biodegradable.

Physical/Chemical:  
Not available.

Other:  
Not available.

## \*\*\*\* SECTION 13 - DISPOSAL CONSIDERATIONS \*\*\*\*

Dispose of in a manner consistent with federal, state, and local regulations.  
RCRA D-Series Maximum Concentration of Contaminants: Not listed.  
RCRA D-Series Chronic Toxicity Reference Levels: Not listed.  
RCRA F-Series: Not listed.  
RCRA P-Series: Not listed.

RCRA U-Series: Not listed.  
Not listed as a material banned from land disposal according to RCRA.

## \*\*\*\* SECTION 14 - TRANSPORT INFORMATION \*\*\*\*

US DOT  
No information available  
IMO  
Not regulated as a hazardous material.  
IATA  
Not regulated as a hazardous material.  
RID/ADR  
Not regulated as a hazardous material.  
Canadian TDG  
No information available.

## \*\*\*\* SECTION 15 - REGULATORY INFORMATION \*\*\*\*

## US FEDERAL

TSCA  
CAS# 90-05-1 is listed on the TSCA inventory.  
Health & Safety Reporting List  
None of the chemicals are on the Health & Safety Reporting List.  
Chemical Test Rules  
None of the chemicals in this product are under a Chemical Test Rule.  
Section 12b  
None of the chemicals are listed under TSCA Section 12b.  
TSCA Significant New Use Rule  
None of the chemicals in this material have a SNUR under TSCA.

## SARA

Section 302 (RQ)  
None of the chemicals in this material have an RQ.  
Section 302 (TPQ)  
None of the chemicals in this product have a TPQ.  
SARA Codes  
CAS # 90-05-1: acute, flammable.  
Section 313  
No chemicals are reportable under Section 313.

## Clean Air Act:

This material does not contain any hazardous air pollutants.  
This material does not contain any Class 1 Ozone depletors.  
This material does not contain any Class 2 Ozone depletors.

## Clean Water Act:

None of the chemicals in this product are listed as Hazardous Substances under the CWA.  
None of the chemicals in this product are listed as Priority Pollutants under the CWA.  
None of the chemicals in this product are listed as Toxic Pollutants under the CWA.

## OSHA:

None of the chemicals in this product are considered highly hazardous by OSHA.

## STATE

Not present on state lists from CA, PA, MN, MA, FL, or NJ.  
California No Significant Risk Level:  
None of the chemicals in this product are listed.

## European/International Regulations

European Labeling in Accordance with EC Directives  
Hazard Symbols: XN  
Risk Phrases:

R 22 Harmful if swallowed.  
R 36/38 Irritating to eyes and skin.

## Safety Phrases:

S 26 In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.

## WGK (Water Danger/Protection)

CAS# 90-05-1: 1

## Canada

CAS# 90-05-1 is listed on Canada's DSL/NDSL List.  
WHMIS: Not available.  
CAS# 90-05-1 is listed on Canada's Ingredient Disclosure List.

## Exposure Limits

## \*\*\*\* SECTION 16 - ADDITIONAL INFORMATION \*\*\*\*

MSDS Creation Date: 11/03/1991 Revision #2 Date: 9/02/1997

The information above is believed to be accurate and represents the best information currently available to us. However, we make no warranty of merchantability or any other warranty, express or implied, with respect to such information, and we assume no liability resulting from its use. Users should make their own investigations to determine the suitability of the information for their particular purposes. In no way shall Fisher be liable for any claims, losses, or damages of any third party or for lost profits or any special, indirect, incidental, consequential or exemplary damages, howsoever arising, even if Fisher has been advised of the possibility of such damages.

---

[Back to product information.](#)

A colourless, corrosive liquid with a pungent odour; weight per ml, about 1.22 g.

**Formic Acid Solution, Non-aqueous** A 5% v/v solution of *anhydrous formic acid* in *chloroform*.

Non-aqueous Formic Acid Solution should be freshly prepared; it is an extremely corrosive material.

**D-Fructose** Laevulose;  $C_6H_{12}O_6 = 180.2$

General reagent grade of commerce.

A white, crystalline powder; melting point, about 103° with decomposition;  $[\alpha]_D^{20}$ , about -92° (10% w/v in water containing 0.05 ml of 5M ammonia).

**L-Fucose** 6-Deoxy-L-galactose;  $C_6H_{12}O_5 = 164.2$

General reagent grade of commerce.

A white powder; melting point, about 140°;  $[\alpha]_D^{20}$ , about -76° (9% w/v in water measured after 24 hours).

**Furfuraldehyde** Furfural; furan-2-aldehyde;

$C_5H_4O_2 = 96.09$

General reagent grade of commerce.

A colourless or pale brownish-yellow, oily liquid; boiling point, about 162°; weight per ml, about 1.16 g.

**D-Galactose**  $C_6H_{12}O_6 = 180.2$

General reagent grade of commerce.

A white, crystalline powder; melting point, about 164°;  $[\alpha]_D^{20}$ , about +80° (10% w/v in water).

**Gallic Acid** 3,4,5-Trihydroxybenzoic acid;  $C_7H_6O_5 \cdot H_2O = 188.1$

General reagent grade of commerce.

Melting point, about 260°.

**Gelatin** Of the British Pharmacopœia.

**Gelatin, Pancreatic Digest of**

Microbiological reagent grade of commerce.

**Gitoxin**  $C_{41}H_{64}O_{14} = 781.0$

General reagent grade of commerce.

A white, crystalline powder; melting point, about 283°, with decomposition;  $[\alpha]_D^{20}$ , about +22° (0.5% w/v in a mixture of equal volumes of chloroform and methanol).

Complies with the following test.

**HOMOGENEITY** Carry out test A for Identification described under *Digitalis Leaf* applying to the chromatoplate a solution containing only the reagent being examined. The chromatogram shows only one spot.

**D-Glucose** Dextrose;  $C_6H_{12}O_6 = 180.2$

Analytical reagent grade of commerce.

A white, crystalline or granular powder;  $[\alpha]_D^{20}$ , about +52.5° (10% w/v in water containing 0.2 ml of 5M ammonia).

**D-Glucose Monohydrate**  $C_6H_{12}O_6 \cdot H_2O = 198.2$

General reagent grade of commerce.

Colourless crystals or a white to cream, crystalline powder;  $[\alpha]_D^{20}$ , about +52.5° (10% w/v in water containing 0.2 ml of 5M ammonia).

**Glycerol** Propane-1,2,3-triol;  $HOCH_2 \cdot CHOH \cdot CH_2OH = 92.10$

Analytical reagent grade of commerce.

A colourless viscous liquid; weight per ml, about 1.26 g.

**Glycerol (85%)** Glycerol containing 12.0 to 16.0% w/w of water; weight per ml, 1.22 to 1.24 g.

**Glycerol Triacetate** Triacetin;  $C_9H_{14}O_6 = 218.2$

General reagent grade of commerce.

A colourless liquid; weight per ml, about 1.16 g.

**Glycine** Aminoacetic acid;  $H_2NCH_2 \cdot CO_2H = 75.1$

Analytical reagent grade of commerce.

**Glycollic Acid** Hydroxyacetic acid;  $HOCH_2 \cdot CO_2H = 76.05$

General reagent grade of commerce.

Slightly hygroscopic crystals; melting point, about 80°.

**Glycyrrhetic Acid** Glycyrrhetic acid; a mixture of  $\alpha$ - and  $\beta$ -isomers with the  $\beta$ -isomer predominating;

$C_{30}H_{46}O_4 = 470.7$

General reagent grade of commerce.

A white to brownish-yellow powder; melting point, about 292°, with decomposition;  $[\alpha]_D^{20}$ , about +160° (1% w/v in chloroform).

**$\beta$ -Glycyrrhetic Acid** 3 $\beta$ -Hydroxy-11-oxo-18 $\beta$ ,20 $\beta$ -olean-12-enoic acid;  $C_{30}H_{46}O_4 = 470.7$

General reagent grade of commerce.

Melting point, about 293°;  $[\alpha]_D^{20}$ , about +170° (1% w/v in chloroform).

**Glyoxal Bis(2-hydroxyanil)** Bis(2-hydroxyphenylimino)-ethane;  $C_{14}H_{12}N_2O_2 = 240.3$

General reagent grade of commerce.

Melting point, about 200°.

**Glyoxal Sodium Bisulphite**

$(HOCH \cdot SO_3Na)_2 \cdot H_2O = 284.2$

General reagent grade of commerce.

A white or cream powder.

**Gonadotrophin, Chorionic**

General reagent grade of commerce.

A white or almost white, amorphous powder.

**Gonadotrophin, Serum**

General reagent grade of commerce.

A white or pale grey, amorphous powder.

**Green S CI 44090; E142; lissamine green; acid brilliant green BS**

Indicator grade of commerce.

**Guaiacol** *o*-Methoxyphenol;  $CH_3O \cdot C_6H_4 \cdot OH = 124.1$

General reagent grade of commerce.

Colourless or pale yellow or pink crystals with an aromatic odour; melting point, about 28°.

**Guaiacol Solution** A 5% w/v solution of *guaiacol* in *ethanol* (96%).

Guaiacol Solution should be protected from light.

**Guaiacum Resin** Resin obtained from the heartwood of *Guaiacum officinale* L. and *Guaiacum sanctum* L.

Reddish-brown or greenish-brown, glassy fragments.

**Guaiacum Tincture** Macerate in a stoppered flask 20 g of *guaiacum resin* with 100 g of *ethanol* (80%) for 24 hours, shaking occasionally, and filter.

**Guaiazulene** 1,4-Dimethyl-7-isopropylazulene;  $C_{15}H_{18} = 198.3$

General reagent grade of commerce.

Dark blue crystals or a blue liquid; melting point, about 29°.

Guaiazulene should be protected from light and air.

**Guanine** 2-Aminopurin-6-one;  $C_5H_4N_2O = 151.1$

General reagent grade of commerce.

**Heavy Metals Masking Solution** To 2.0 ml of 2M *ammonia* add, in the following order, 1.5 ml of a 5% w/v solution of *ammonium oxalate*, 15 ml of a 5% w/v solution of *potassium cyanide*, 45 ml of a 10% w/v solution of *sodium acetate*, 120 ml of a 50% w/v solution of *sodium thiosulphate*, 75 ml of a 10% w/v solution of *sodium acetate* and 35 ml of 1M *hydrochloric acid*.

Heavy Metals Masking Solution should be prepared immediately before use.

## PREPARATIONS

**Euphorbia Liquid Extract** (B.P.C. 1949). Ext. Euphorb. Liq. 1 in 1: prepared by percolation with alcohol (45%). *Dose*: 0.12 to 0.3 ml.

**Mist. Euphorb. Co.** (N.F. 1939). Euphorbia liquid extract 0.6 ml, potassium iodide 450 mg, sodium bromide 450 mg, glyceryl trinitrate solution 0.06 ml, ethereal lobelia tincture 0.4 ml, water to 15 ml. *Dose*: 15 ml.

**AMENDED FORMULA.** Euphorbia liquid extract 0.5 ml, potassium iodide 450 mg, sodium bromide 450 mg, glyceryl trinitrate solution 0.05 ml, ethereal lobelia tincture 0.4 ml, water to 10 ml.—*Compendium of Past Formulae 1933 to 1966*, London, The National Pharmaceutical Union, 1969.

**NOTE.** **Euphorbium** (B.P.C. 1934, *Neth.P., Nord.P., Port.P., Span.P., Swiss.P.*) is the dried latex from the stem of *Euphorbia resinifera*. It is emetic and powerfully purgative but it is not used internally on account of its violent action and its tendency to cause acute nephritis. The powder is violently sternutatory. Externally, it acts as a vesicant and was used for this purpose in veterinary medicine.

**Garlic** (B.P.C. 1949, *Span. P.*). Allium; Ail.

The fresh bulb of *Allium sativum* (Liliaceae). It has a very strong and disagreeable odour and a strongly pungent and persistent taste. It yields 0.1 to 0.3% of a volatile oil containing allyl propyl disulphide and diallyl disulphide. **Stored** in a cool dry place with free access of air it may be kept for about 6 months after harvesting.

Garlic has expectorant, diaphoretic, disinfectant, and diuretic properties, and the juice was formerly used alone or in a syrup in the treatment of pulmonary conditions. **Precautions**: administration of preparations of garlic to children is dangerous and fatalities have been recorded. *Dose*: 2 to 8 g.

The larvicidal principles of garlic active against the *Culex* mosquito were found to be diallyl di- and trisulphides. Natural and synthetic samples proved fatal at 5 ppm.—S. V. Amonkar and A. Banerji, *Science, Wash.*, 1971, 174, 1343.

A report of allergic contact dermatitis to garlic.—E. Bleumink *et al.*, *Br. J. Derm.*, 1972, 87, 6.

Garlic juice and the extracted essential oil prevented the hyperlipaemia and blood coagulation changes following fat ingestion in 5 healthy subjects.—A. Bordia and H. C. Bansal (letter), *Lancet*, ii/1973, 1491.

**HYPERTENSION.** In 5 consecutive cases of hypertension, garlic reduced the blood pressure to satisfactory levels.—V. Srinivasan (letter), *Lancet*, ii/1969, 800.

## PREPARATIONS

**Garlic Juice** (B.P.C. 1949). Succus Allii. Bruise garlic 80 g and express the juice; mix the marc with water 20 ml and again express the liquid; repeat the operation until the volume of the mixed juice and washings amounts to 80 ml, and add alcohol (90%) 20 ml; allow to stand for 14 days, and decant or filter. *Dose*: 2 to 4 ml.

**Garlic Syrup** (B.P.C. 1949). Syr. Allii. Garlic juice 20 ml, sucrose 80 g, dilute acetic acid 20 ml, water 20 ml. *Dose*: 2 to 8 ml.

**Grindelia** (B.P.C. 1949). *Grindelia Robusta*; Gum Plant; Gumweed; Tar Weed.

**Foreign Pharmacopoeias**: In *Span.* In *Belg.* and *Braz.* which allow also the dried leaves and flowering tops of the marsh gumweed, *G. humilis*, and of the curly-cup gumweed, *G. squarrosa*. In *Fr.* and *Port.* which allow also *G. squarrosa*.

The dried leaves and flowering tops of the field gumweed, *Grindelia camporum* (Compositae) containing not less than 20% of alcohol (90%)—soluble extractive. **Store** in a cool dry place.

*Grindelia* has expectorant properties and has been stated to exert a spasmolytic effect. It has been used as a liquid extract in the treatment of asthma and bronchitis. Large doses sometimes cause renal irritation. Its nauseous taste may be masked with chloroform or glycerol.

## PREPARATIONS

**Grindelia Liquid Extract** (B.P.C. 1949). Ext. Grindel. Liq. *Grindelia* 100 g is exhausted by percolation with alcohol (90%), the alcohol is removed by distillation, and the residue is dissolved in water 50 ml to which 10 g of sodium bicarbonate has previously been added; after effervescence has ceased, the solution is adjusted to 100 ml with alcohol (90%) and filtered. *Dose*: 0.6 to 1.2 ml.

**Guaiaicol** (B.P.C. 1949). Gaiacol; Methyl Catechol.

**Foreign Pharmacopoeias**: In *Arg.*, *Braz.*, *Chil.*, *Fr.*, *It.*, *Mex.*, *Port.*, *Roum.*, *Span.*, and *Swiss.*

A colourless or almost colourless oily liquid or crystals with a penetrating aromatic odour and a caustic taste, obtained as a liquid by fractional distillation of wood-tar creosote or, usually as crystals, by synthesis.

The main constituent is *o*-methoxyphenol,  $\text{CH}_3\text{O.C}_6\text{H}_4.\text{OH} = 124.1$ . Wt per ml (liquid) about 1.12 g; m.p. (crystals) about 28°. It tends to become yellowish on exposure to light.

**Soluble** 1 in 80 of water; miscible with alcohol, chloroform, ether, glacial acetic acid, and fixed and volatile oils; soluble 1 in 1 of glycerol but separates out on the addition of water. **Incompatible** with ferric salts. **Protect** from light.

Guaiaicol has disinfectant properties similar to those of creosote. It has been used as an expectorant. **Toxic effects**: as for Phenol, p. 529. *Dose*: 0.3 to 0.6 ml.

**Guaiaicol Carbonate** (B.P.C. 1949). Duotal.  $(\text{CH}_3\text{O.C}_6\text{H}_4.\text{O})_2\text{CO}$  274.3.

**Foreign Pharmacopoeias**: In *Chil.*, *Port.*, and *Span.*

Guaiaicol carbonate is the carbonic ester of guaiaicol. It is a white, almost odourless, tasteless, crystalline powder. M.p. 83° to 88°. **Insoluble** in water; soluble 1 in 70 of alcohol and 1 in 20 of ether; readily soluble in chloroform; slightly soluble in glycerol and fixed oils. It is decomposed by alcoholic potassium hydroxide solution and guaiaicol separates from the solution on the addition of excess acid.

Guaiaicol carbonate has the actions of guaiaicol but is less irritant; it liberates guaiaicol slowly and incompletely in the intestines, the larger part passing through the alimentary tract unchanged. *Dose*: 0.3 to 1 g.

**Guaiphenesin** (B.P.C.). Guaiaicyl Glyceryl Ether; Guaiaicol Glycerol Ether; Guaifenesin (U.S.N.F.); Glyceryl Guaiaicolate; Glycerylguayacolum. 3-(*o*-Methoxyphenoxy)propane-1,2-diol.  $\text{C}_{10}\text{H}_{14}\text{O}_4 = 198.2$ .

**Foreign Pharmacopoeias**: In *Cz.* and *Roum.* Also in *U.S.N.F.*

**Dose**: 100 to 200 mg every 2 to 4 hours.

White odourless or almost odourless crystals or crystalline aggregates with a bitter taste. M.p. 80° to 82°.

**Soluble** 1 in 33 of water at 20°, 1 in 11 of alcohol and 1 in 10 of chloroform, and 1 in 200 of ether; soluble 1 in 15 of glycerol with warming, 1 in 15 of propylene glycol, and 1 in 80 of sorbitol syrup. A 2% solution in water has a pH of 5 to 7 and is clear and colourless. Aqueous solutions are stable and may be sterilised by autoclaving. **Store** in airtight containers.

**Toxic Effects and Precautions.** Side-effects are rare with guaiphenesin. Gastro-intestinal discomfort and drowsiness have been reported.

A metabolite of guaiphenesin was found to produce an apparent increase in urinary 5-hydroxyindoleacetic acid, and guaiphenesin could thus interfere with the diagnosis of the carcinoid syndrome. Asthmatic patients being evaluated for the carcinoid syndrome should therefore discontinue any preparation containing guaiphenesin for 24 hours before the collection of urine specimens for the determination of 5-hydroxyindoleacetic acid. Acetanilide, mephenesin, and methocarbamol had been reported to cause similar false positive reactions, and hexamine methanolate and some phenothiazine derivatives to cause false negative reactions.—A. T. Pedersen *et al.*, *J. Am. med. Ass.*, 1970, 211, 1187. See also P. D. Reeme, *Hosp. Formul. Mgmt.*, 1970, 5, 15, per *Int. pharm. Abstr.*, 1973, 10, 26.

Hypouricaemia (serum-urate concentrations of less than 20 µg per ml) in 6 patients could have been due to guaiphenesin. Therapeutic doses for 3 days reduced serum urate by up to 30 µg per ml in 4 patients.—C. Ramsdell and W. N. Kelley, *Ann. intern. Med.*, 1973, 78, 239.

**Absorption and Fate.** Guaiphenesin is readily absorbed from the gastro-intestinal tract. It is rapidly metabolised and excreted in the urine.

Guaiphenesin was rapidly absorbed from the gastro-intestinal tract. Blood concentrations of 1.4 µg per ml occurring 15 minutes after a dose of 600 mg in 3 healthy fasting men. It was rapidly eliminated from the circulation, having a half-life of 1 hour, and was not detectable in the blood after 8 hours.—W. R. Maynard and R. B. Bruce, *J. pharm.*, 1970, 59, 1346.

The major urinary metabolite of guaiphenesin was identified as 3-(*o*-methoxyphenoxy)lactic acid.—W. J. A. VandenHeuvel *et al.*, *J. pharm. Sci.*, 1972, 61, 1997.

**Uses.** Guaiphenesin is reported to reduce the viscosity of tenacious sputum and is used as an expectorant in cough linctus and tablets.

When given by mouth or by injection in large doses, guaiphenesin has a relaxant effect on skeletal muscle similar to that of mephenesin which it closely resembles structurally. This effect is not produced by the doses normally employed in the treatment of cough.

tics

**teine** (2948-y)

(rINN).  
rahydro-2-oxo-3-thienylcarbamoyl)methylthio)-  
S  
46 4.

ne is being studied for use as a mucolytic

**lictyon** (2012-e)

Balm; Yerba Santa.  
8013-08-9.

leaves of *Eriodictyon californicum* (Hydrophyl-

tyon has been used as an expectorant. It has  
en used to mask the taste of bitter drugs.

**ications**

if preparations are listed below; details are given in Part 3.

**itary Preparations**

gredient preparations. Ger.: Mistelan†; Ital.: Bronco-

**yl Cysteine Hydrochloride**

(2-amino-3-mercaptopropionate hydrochloride).  
NO<sub>2</sub>S.HCl = 185.7.  
— 3411-58-3 (ethyl cysteine); 868-59-7 (ethyl  
ne hydrochloride).

l cysteine hydrochloride is a mucolytic agent  
p.1059) used in the treatment of disorders of the  
tract associated with excessive or vis-  
m daily dose of 600 to 900 mg has been  
n in 2 or 3 divided doses.

**parations**

s of preparations are listed below; details are given in Part 3.

**rietary Preparations**

Tudixant†.

**hyl Orthoformate** (5618-z)

de Kay; Triethoxymethane. Triethyl orthoformate.  
1<sub>6</sub>O<sub>3</sub> = 148.2.  
— 122-51-0.  
macopoeias. In Fr.

yl orthoformate is a cough suppressant (see  
059). It is reported to be a respiratory antispas-  
dic and is administered by mouth or rectally.

**eparations**

mes of preparations are listed below; details are given in Part 3.

**roprietary Preparations**

ig.: Aethone; Fr.: Aethone.

ulti-ingredient preparations. Switz.: Rectoquintyl; Recto-  
milyl-Prométhazine.

**edrilate** (5619-x)

ndilate (rINN).  
ndilatum; UCB-3928. 1-Methyl-3-morpholinopropyl perhy-  
o-4-phenylpyran-4-carboxylate.  
2<sub>6</sub>H<sub>29</sub>NO<sub>4</sub> = 347.5.  
AS — 23271-74-1.

edrilate is a cough suppressant (see p.1059) which  
as given by mouth as the maleate in doses of  
50 e to six times daily.

**Preparations**

Names of preparations are listed below; details are given in Part 3.

**Proprietary Preparations**

S.Afr.: Corbar S; Dykatuss "S".

Multi-ingredient preparations. Ger.: Duotalt†.

**Fominoben Hydrochloride** (5620-z)

Fominoben Hydrochloride (rINN).  
PB-89. 3'-Chloro-2'-[N-methyl-N-(morpholinocarbonyl-  
yl)aminomethyl]benzanilide hydrochloride.  
C<sub>21</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>3</sub>.HCl = 438.4.  
CAS — 18053-31-1 (fominoben); 24600-36-0 (fominoben  
hydrochloride).

Fominoben hydrochloride is a centrally acting  
cough suppressant (see p.1059) which is also report-  
ed to have respiratory stimulant properties. It is  
en in doses of 160 mg two or three times daily  
mouth; it has also been given by slow intravenous  
injection.

**References**

1. Sasaki T. et al. Effects of the antitussive fominoben (PB89) on  
hypoxia in chronic obstructive lung disease: comparison  
dextromethorphan using a double-blind method. *J Int Med* 1985;  
13: 96-101.

**Preparations**

Names of preparations are listed below; details are given in Part 3.

**Proprietary Preparations**

Ger.: Noleptan†; Ital.: Tenont†; Spain: Broncomenalt†; Taiwan:  
Tosifar.

Multi-ingredient preparations. Ger.: Broncho-Noleptan†.

**Glaucine** (19251-g)

Boldine Dimethyl Ether; DL-832 (dl-glaucine phosphate);  
Glaucine; MDL-832 (dl-glaucine phosphate). DL-1,2,9,10-  
tramethoxyaporphine.  
C<sub>21</sub>H<sub>25</sub>NO<sub>4</sub> = 355.4.  
CAS — 5630-11-5 (dl-glaucine); 73239-87-9 (dl-glaucine  
phosphate); 475-81-0 (d-glaucine); 5996-06-5 (d-glaucine  
hydrabromide).

Glaucine is a centrally acting cough suppressant  
(see p.1059) which has been studied as the phos-  
phate.

d-Glaucine has been used as the hydrobromide and  
the hydrochloride as a cough suppressant in eastern  
Europe. It has been obtained from *Glaucium flavum*  
(Papaveraceae).

**References**

1. Redpath JBS, Pleuvry BJ. Double-blind comparison of the res-  
piratory and sedative effects of codeine phosphate and dl-  
glaucine phosphate in human volunteers. *Br J Clin Pharmacol* 1982;  
14: 555-8.  
2. Rühle KH, et al. Objective evaluation of dextromethorphan and  
glaucine as antitussive agents. *Br J Clin Pharmacol* 1984; 17:  
521-4.  
3. Gastpar H, et al. Efficacy and tolerability of glaucine as an  
antitussive agent. *Curr Med Res Opin* 1984; 9: 21-7.

**Guacetal** (12801-w)

Guacetal (rINN).  
Acetylsalicylic Acid Guaiacol Ester. o-Methoxyphenyl salicylic  
acetate.  
C<sub>16</sub>H<sub>14</sub>O<sub>5</sub> = 286.3.  
CAS — 55482-89-8.

Guacetal has been used in respiratory disorders  
as an expectorant (see p.1059). It has also been used  
as an antipyretic to reduce fever, the more usual treat-  
ment of which is discussed on p.2. Doses of 500 mg  
have been administered by mouth two to three times  
daily. It has also been administered rectally.

**Preparations**

Names of preparations are listed below; details are given in Part 3.

**Proprietary Preparations**

Ital.: Balsacetyl; Broncaspin; Guaiaspir; Guajabronc; Pronio-

**Guaiacol** (2016-z)

Guaiacol; Methyl Catechol.  
CAS — 90-05-1 (guaiacol); 553-17-3 (guaiacol carbon-  
ate); 60296-02-8 (calcium guaiacolglycolate); 4112-89-4  
(guaiacol phenylacetate).  
Pharmacopoeias. In Belg., Fr., and Swiss. Fr. also includes Guai-  
acol Carbonate.

The main constituent of guaiacol is 2-methoxyphenol.  
CH<sub>3</sub>O.C<sub>6</sub>H<sub>4</sub>.OH = 124.1.

Guaiacol has disinfectant properties and has been  
used as an expectorant (see p.1059).

Adverse effects are similar to those of Phenol,  
p.1141.

A wide range of salts and derivatives of guaiacol  
have been used similarly including the carbonate,  
cinnamate, ethylglycolate, calcium and sodium gly-  
colates, phenylacetate, and phenylbutyrate. See also  
Guaiaphenesin, p.1069 and Potassium Guaiacolsul-  
fonate, p.1074.

**Preparations**

Names of preparations are listed below; details are given in Part 3.

**Proprietary Preparations**

Ger.: Anastil†.

Multi-ingredient preparations. Austral.: Waterbury's Com-  
pound; Belg.: Baume Dalet; Ebexolt†; Eucalyptine Le Brun; Eucal-  
yptine Pholcodine Le Brun; Inalpin (Canada); Creol-Rectal; Demo-  
cineol†; Dolodent†; Omni-Tuss; Valda; Eire: Valda; Fr.: Baume  
Dalet; Biocetylptol; Bi-Qui-Nol; Bronchodermine; Bronchorectine  
Dalet; Camphocetylptol Quinine†; Camphocetylptol Simple†;  
Citral; Camphocetylptol Quinine†; Elixir Dupeyroux†; Essence Algèrenne; Eu-  
calyptine Aspirine Quinine†; Eucalyptine Le Brun; Eucalyptine  
Pholcodine; Eucalyptospirine†; Gaiarsol; Pulmoserum; Recto-  
pédrol; Sirop Bojn; Tieucaly†; Valda (Ger.) Anastil Camphert;  
Anastil†; Cobed†; Dalet-Balsam; Pertux†; Transpulmin†; Zynedo-  
Bt; Zynedo-K† (Ital.) Auncovitt†; Biopulmin†; Bronco Valda†;  
Eucalyptina; Fostoguaicol; Glicocinnamina†; Guaiadomust†;  
Katzama Balsamico†; Lactocool; Lipobalsamo; Otocain†; Otor-  
mon F (Femmine)†; S-Afr.: Cocilix (Spain); Anginum†; Anufer-  
in Balsamico†; Bimoxi Mucolitico; Bronco Aseptilex; Bronco  
Aseptilex Fuerte; Bronco Aseptilex Tetra†; Broncolite†; Bronqui-  
mar; Bronquimar NF†; Bronquimar Vit A; Edusan Fie Rectal; Eu-  
calyptospirine; Eucalyptospirine Lact; Mahoterpen; Pulmo Grey  
Balsam; Pulmo Hidratol†; Tos Mac (Spain) Bronchodermine;  
Bronchorectine; Carmol "blanche"†; Liberol; Rectoseptal-Néo  
Pholcodine; Rectoseptal-Néo simple (UK); Dragon Balm; Pulmo  
Bailey; Valda (USA) Methagual.

**Guaiapate** (12803-j)

Guaiapate (USAN, rINN).  
MG-5454. 1-[2-[(2-o-Methoxyphenoxyethoxy)ethoxy]e-  
thyl]piperidine.  
C<sub>18</sub>H<sub>29</sub>NO<sub>4</sub> = 323.4.  
CAS — 852-42-6.

Guaiapate has been used as a cough suppressant. It  
is reported to have central actions.

**Guaietolin** (12795-v)

Guaietolin (rINN).  
Glycerylguethol; Glyguetol. 3-(2-Ethoxyphenoxy)propane-  
1,2-diol.  
C<sub>17</sub>H<sub>16</sub>O<sub>4</sub> = 212.2.  
CAS — 63834-83-3.

Guaietolin is an analogue of guaiaphenesin which is  
used as an expectorant (see p.1059). It has been given  
by mouth in doses of 300 to 600 mg two to three  
times daily.

**Preparations**

Names of preparations are listed below; details are given in Part 3.

**Proprietary Preparations**

Fr.: Guéthural.

**Guaimesal** (1749-r)

Guaimesal (rINN).  
(1)-2-(o-Methoxyphenoxy)-2-methyl-1,3-benzodioxan-4-  
one.  
C<sub>14</sub>H<sub>14</sub>O<sub>5</sub> = 286.3.  
CAS — 81674-79-5.

Guaimesal is reported to have anti-inflammatory,  
antipyretic, analgesic, and mucolytic properties and  
has been given by mouth in a usual dose of 500 mg  
two to three times daily as an adjunct in the treat-  
ment of acute and chronic infections of the respira-  
tory tract. It has also been administered rectally in  
suppositories.

Guaimesal has been reported to improve fever, cough fre-  
quency and intensity, and sputum viscosity in patients with  
acute or chronic bronchitis. However, as stated in the discus-  
sion on the management of cough (see p.1059) mucolytics are

The symbol † denotes a preparation no longer actively marketed

generally consider  
more effective no  
p.1567.

1. Jager EGH. Dou-  
tion of guaimesal

**Preparation:**  
Names of prepara-  
**Proprietary Prep**  
Ital.: Bronteril.

**Guaiphen**

Guaiaphenesin (BA)  
Glyceril Guaiacol  
Ether; Guaiaeyl (C)  
Guaifenesina; Gua  
3-(2-Methoxyphenoxy)  
C<sub>10</sub>H<sub>14</sub>O<sub>4</sub> = 198  
CAS — 93-14-1.  
Pharmacopoeias. In  
Port., Swiss, and US  
The standards of P  
ties to the Conve  
macopoeia. see p

A white or slight  
a slight character  
BP solubilities a  
cohol and in chlo  
bilities are: solub  
in chloroform, an  
glycerol. A 1% sc  
syrup has a pH of

**Adverse Effe**

Gastro-intestir  
reported with  
nausea and vo.

**Pharmacok**

Guaiaphenesin  
tract. It is met:

**Uses and A**

Guaiaphenesin  
Guaiaphenesin s  
tenacious sputu  
p.1059). It has  
to 400 mg even  
may be given  
dren aged 2 to  
It has been us

**Infertility.** Gua  
tility in women  
cervical mucus.  
mention of this t  
1. Check JH, et al  
esin. *Fertil Ster*

**Respiratory** d  
tions available  
in was an effec  
discussed on p.  
1. Thomas J. Gu  
tive. *Aust J Ph*

**Uricosuric ac**  
rum-urate conc  
effect in these p  
ered to be clinic  
1. Ramsdell CM.  
*J Rheumatol* 1  
2. Matheson CE,  
tion on serum u  
4.

**Preparati**

Names of prepa  
**Official Prepa**  
USP 23: Dyph  
Guaifenesin Tal  
Guaiaphenesin at  
Guaifenesin Car  
ride, and Dextre  
in Syrup; Guai  
Capsules; Theoi  
**Proprietary P.**  
Aust.: Guafen; S  
er: Austral.: R-  
Expectorant; C  
Expectorant; R  
posyrup expei  
Nephulon G; R  
Robitussin; S.A

Juice (B.P.C. 1949). Succus Allii. Bruise garlic and express the juice; mix the marc with water and again express the liquid; repeat the operation until the volume of the mixed juice and washings is 80 ml, and add alcohol (90%) 20 ml; allow for 14 days, and decant or filter. Dose. 2 to 3 ml.

Syrup (B.P.C. 1949). Syr. Allii. Garlic juice sucrose 80 g, acetic acid (6 per cent) 20 ml, 20 ml. Dose. 2 to 8 ml.

Gum Plant; Gumweed; Tar

*Grindelia* (B.P.C. 1949). In Belg. and Fr. which also allow *G. robusta*, and *G. squarrosa*. Span. and Port. also allow *G. robusta*; Port. also allows *G. squarrosa*.

Dried leaves and flowering tops of *Grindelia campocroci* (Compositae) containing not less than 20% of alcohol-soluble extractive. Store in a cool dry place.

*Grindelia* has expectorant properties and has been stated to exert a spasmolytic effect. It has been used as a tincture or a syrup in the treatment of asthma and bronchitis. Large doses sometimes cause renal disturbances. Its nauseous taste may be masked with chloroform or glycerol.

#### Preparations

Liquid Extract (B.P.C. 1949). Ext. Grindelia. *Grindelia* 100 g is exhausted by percolation with alcohol (90%), the alcohol is removed by distillation, and the residue is dissolved in water 50 ml to which sodium bicarbonate has previously been added; effervescence has ceased, the solution is adjusted to pH 7 with alcohol (90%) and filtered. Dose. 0.6 to 1 ml.

#### 26-z

Guaiacol (B.P.C. 1949). Guaiacol; Methyl Catechol.  $C_8H_8O_2$  — 90-05-1 (2-methoxyphenol).

Pharmacopoeias. In Arg., Fr., It., Mex., Port., Roum., and Swiss.

Colourless or almost colourless oily liquid or crystals with a penetrating aromatic odour and a caustic taste, obtained as a liquid by fractional distillation of wood-tar or, usually as crystals, by synthesis.

The main constituent is 2-methoxyphenol,  $C_8H_8O_2$ ,  $M_p = 124.1$ . Wt per ml (liquid) about 1.22 g; m.p. (crystals) about 28°. It tends to become viscous on exposure to light.

Soluble 1 in 80 of water; miscible with alcohol, chloroform, ether, glacial acetic acid, and fixed and volatile oils; soluble 1 in 1 of glycerol but separates out on the addition of water. Incompatible with ferric salts, ammonia, menthol, and chloral hydrate. Protect from light.

Guaiacol has disinfectant properties similar to those of phenol. It has been used as an expectorant in doses of 0.3 to 0.6 ml. Adverse effects are similar to those of phenol, p.571.

#### 267-c

Guaiacol Carbonate (B.P.C. 1949). Duotal. Bis(2-methoxyphenyl) carbonate.  $(C_8H_7O_2)_2CO = 274.3$ .  $CS = 553-17-3$ .

Pharmacopoeias. In Port. and Span.

Guaiacol carbonate is the carbonic ester of guaiacol. It is a white, almost odourless, tasteless, crystalline powder. M.p. 83° to 88°. Practically insoluble in water; soluble 1 in 70 of alcohol and 1 in 20 of ether; readily soluble in chloroform; slightly soluble in glycerol and fixed oils. It is decomposed by alcoholic potassium hydroxide solution and guaiacol separates from the solution on the addition of excess acid.

Guaiacol carbonate has the actions of guaiacol but is less irritant. It has been used in doses of 0.3 to 1 g. It liberates guaiacol slowly and incompletely in the intes-

tines, the larger part passing through the alimentary tract unchanged.

2018-k

Guaiphenesin (B.P.). Guaiacyl Glyceryl Ether; Guaiacol Glycerol Ether; Guaifenesin (U.S.P.); Glyceryl Guaiacolate; Glycerylguaiacolum; Guaiacolum Glycerolatum. 3-(2-Methoxyphenoxy)propane-1,2-diol.  $C_{10}H_{14}O_4 = 198.2$ .

CS — 93-14-1.

Pharmacopoeias. In Aust., Br., Cz., Roum., and U.S.

White or slightly grey crystals or crystalline aggregates, odourless or with a slight characteristic odour and with a bitter taste. M.p. 78° to 82° with a range of not more than 3°.

Soluble 1 in 33 of water at 20°, 1 in 11 of alcohol and of chloroform, and 1 in 100 of ether; soluble 1 in 15 of glycerol with warming, 1 in 15 of propylene glycol, and 1 in 80 of sorbitol syrup. A 2% solution in water has a pH of 5 to 7. Aqueous solutions are stable and may be sterilised by autoclaving. Store in airtight containers.

Adverse Effects and Precautions. Gastro-intestinal discomfort and drowsiness have been reported. Very large doses cause nausea and vomiting.

A metabolite of guaiphenesin was found to produce an apparent increase in urinary 5-hydroxyindoleacetic acid, and guaiphenesin could thus interfere with the diagnosis of the carcinoid syndrome. Patients being evaluated for the carcinoid syndrome should therefore discontinue any preparation containing guaiphenesin for 24 hours before the collection of urine specimens for the determination of 5-hydroxy indoleacetic acid. Acetanilide, mephensin, and methocarbamol had been reported to cause similar false positive reactions, and hexamine mandelate and some phenothiazine derivatives to cause false negative reactions.— A. T. Pedersen et al., *J. Am. med. Ass.*, 1970, 211, 1184. See also P. D. Reeme, *Hosp. Formul. Mgmt.*, 1970, 5, 15, per *Int. pharm. Abstr.*, 1973, 10, 26.

Hypouricaemia (serum-urate concentrations of less than 20 µg per ml) in 6 patients could have been due to guaiphenesin. Therapeutic doses for 3 days reduced serum urate by up to 30 µg per ml in 4 patients.— C. M. Ramsdell and W. N. Kelley, *Ann. intern. Med.*, 1973, 78, 239.

Absorption and Fate. Guaiphenesin is readily absorbed from the gastro-intestinal tract. It is rapidly metabolised and excreted in the urine.

Guaiphenesin was rapidly absorbed from the gastro-intestinal tract, blood concentrations of 1.4 µg per ml occurring 15 minutes after a dose of 600 mg in 3 healthy fasting men. It was rapidly eliminated from the circulation, having a half-life of 1 hour, and was not detectable in the blood after 8 hours.— W. R. Maynard and R. B. Bruce, *J. pharm. Sci.*, 1970, 59, 1346.

The major urinary metabolite of guaiphenesin was identified as β-(2-methoxyphenoxy)lactic acid.— W. J. A. VandenHeuvel et al., *J. pharm. Sci.*, 1972, 61, 1997.

Uses. Guaiphenesin is reported to reduce the viscosity of tenacious sputum and is used as an expectorant. It has been given in doses of 100 to 200 mg every 2 to 4 hours.

When given by mouth or by injection in large doses, guaiphenesin has a relaxant effect on skeletal muscle similar to that of mephensin which it closely resembles structurally, but this effect is not produced by the doses normally employed in the treatment of cough.

Guaiphenesin was no better than water in lowering the viscosity of 27 sputum specimens obtained from chronic bronchitics. Doses of 0.8 to 1.6 g daily had no effect on sputum or respiratory function when compared with placebo in 11 patients with chronic bronchitis.— S. R. Hirsch et al., *Chest*, 1973, 63, 9.

From a study in 239 patients it was reported that guaiphenesin reduced cough frequency and intensity in patients with dry or productive cough, and helped to thin sputum, when compared to placebo.— R. E. Robinson et al., *Robins, Curr. ther. Res.*, 1977, 22, 284.

A report of a double-blind crossover study in 19 patients with chronic bronchitis showed that guaiphenesin was

not significantly better than a placebo in aiding clearance of secretion from the lungs.— D. B. Yeates et al., *Am. Rev. resp. Dis.*, 1977, 115, Suppl. 4, 182.

Effects on blood. A dose of 200 mg of guaiphenesin was found to prolong the activated-plasma clotting time in 22 healthy volunteers. The same dose, given to 12 healthy volunteers, was found to reduce platelet adhesiveness significantly.— R. D. Eastham and E. P. Griffiths, *Lancet*, 1966, 1, 795.

Guaiphenesin 200 mg given as a single dose to 5 healthy subjects was associated with transient abnormality in platelet aggregation patterns determined 1 hour after ingestion, showing some inhibition of secondary aggregation but less marked than that observed in other subjects given chlorpromazine or aspirin. Mean bleeding times as determined by a modified Ivy technique were prolonged by single doses of aspirin but were not affected by guaiphenesin; thrice-daily doses of indomethacin given for 3 days caused some prolongation.— G. R. Buchanan et al., *Am. J. clin. Path.*, 1977, 68, 355.

#### Preparations

Guaifenesin Capsules (U.S.P.). Capsules containing guaiphenesin. Store in airtight containers.

Guaifenesin Syrup (U.S.P.). A syrup containing guaiphenesin and alcohol 3 to 4%. pH 2.3 to 3. Store in airtight containers.

Guaifenesin Tablets (U.S.P.). Tablets containing guaiphenesin. Store in airtight containers.

Guaiphenesin Linctuses. (1) Lemon-flavoured. Guaiphenesin 2 g, glycerol 10 ml, chloroform spirit 10 ml, menthol 10 mg, compound tartrazine solution 0.2 ml, water 10 ml, modified lemon syrup to 100 ml.

(2) Tolu-flavoured. Guaiphenesin 2 g, glycerol 10 ml, chloroform spirit 10 ml, menthol 10 mg, amaranth solution 1 ml, tolu solution 10 ml, invert syrup 20 ml, syrup to 100 ml.

Modified lemon syrup contains lemon spirit 0.5 ml, citric acid monohydrate 2.5 g, invert syrup 20 ml, syrup to 100 ml.

Both lemon-flavoured and tolu-flavoured guaiphenesin linctuses remained stable for 6 months when stored at temperatures from -5° to 37°.— Pharm. Soc. Lab. Rep. No. P/65/21, 1965. See also G. Smith, *Pharm. J.*, 1966, 1, 165.

#### Proprietary Preparations

Dimotane Expectorant (Robins, UK). Contains in each 5 ml guaiphenesin 100 mg, brompheniramine maleate 2 mg, phenylephrine hydrochloride 5 mg, and phenylpropanolamine hydrochloride 5 mg (suggested diluent, syrup). Dimotane Expectorant DC contains in addition hydrocodone tartrate 1.8 mg in each 5 ml. Dose. 5 to 10 ml four times daily; children, 1 to 3 years, 1 to 2.5 ml; 3 to 6 years, 2.5 to 5 ml; 6 to 12 years, 5 ml.

Dimotane with Codeine (Robins, UK). Contains in each 5 ml guaiphenesin 100 mg, codeine phosphate 10 mg, brompheniramine maleate 2 mg, phenylephrine hydrochloride 5 mg, and phenylpropanolamine hydrochloride 5 mg (suggested diluent, syrup). For cough. Dose. 5 to 10 ml four times daily.

Dimotane with Codeine Paediatric (Robins, UK). Contains in each 5 ml guaiphenesin 50 mg, codeine phosphate 3 mg, brompheniramine maleate 1 mg, phenylephrine hydrochloride 2.5 mg, and phenylpropanolamine hydrochloride 2.5 mg (suggested diluent, syrup). Dose. 3 to 6 years, 5 ml four times daily; 6 to 12 years, 5 to 10 ml.

Exyphen (Norton, UK; Vestric, UK). An elixir containing in each 5 ml guaiphenesin 80 mg, brompheniramine maleate 2 mg, phenylephrine hydrochloride 4.75 mg, and phenylpropanolamine hydrochloride 5 mg. For cough. Dose. 5 to 10 ml four times daily; children, 2.5 to 5 ml three or four times daily.

Noradran Bronchial Syrup (Norma, UK; Farillon, UK). Contains in each 5 ml guaiphenesin 25 mg, diphenhydramine hydrochloride 5 mg, diprophyllyne 50 mg, and ephedrine hydrochloride 7.5 mg. Dose. 10 ml every 4 hours; children over 5 years, 5 ml.

Pholcodone Expectorant (formerly known as Pulmodrine Expectorant) (Medo Chemicals, UK). Contains in each 5 ml guaiphenesin 62.5 mg and methylephedrine hydrochloride 625 µg. Dose. 10 to 20 ml thrice daily; children, 2.5 to 5 ml.

Robitussin (Robins, UK). An expectorant mixture containing in each 5 ml guaiphenesin 100 mg (suggested diluent, syrup). (Also available as Robitussin in Austral., Canad., Ital.).

Robitussin AC (Robins, UK). Contains in each 5 ml guaiphenesin 100 mg, codeine phosphate 10 mg, and pheniramine maleate 7.5 mg (suggested diluent, syrup). For coughs. Dose. 5 to 10 ml four times daily; children, 6 to 12 years, 5 ml.