

ATTACHMENT 9

PART IV.

CLINICAL DOCUMENTATION

HUMET-R Syrup 300 ml

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**University of Medicine and Pharmacy,
Marosvásárhely (Tirgu Mures, Romania)
Department of Occupational Medicine**

HUM 062

**Observations
about workers Exposed to lead in connection with the
administration of the Humet®-R syrup**

(Lecture notes for information supplied in Brashow, Romania)

**Author:
Prof. Sándor Dienes, M.D.**

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OBSERVATIONS ABOUT WORKERS EXPOSED TO LEAD IN CONNECTION WITH THE APPLICATION OF THE HUMET-R SYRUP

Prof Dr Sándor Dienes

UNIVERSITY OF MEDICINE AND PHARMACY, MAROSVÁSÁRHELY (TIRGU MURES, ROMANIA)
DEPARTMENT OF OCCUPATIONAL MEDICINE

Macro and microelements play a primary role in haematopoiesis. Some of the enzymes of the body contain macro and microelements. Their presence is vital. The 'complexon' like physiological effect of some elements is known; based on literature data; first of all the similar role of Magnesium ion is important, especially in the binding of heavy metals (Lead, Mercury, Chromium).

The HUMET-R syrup contains a lot of mineral elements besides humic acid (Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum, and Selenium), which are essential ions for the body. Besides their role in haematopoiesis these ions are known to be part of a lot of enzymes, they have a significant liver protecting effect (Manganese, Selenium), they play an important role in the metabolism of proteins and lipids, and in maintaining the immune-biological balance of the body.

Test material, and methods

We carried out our examinations on the inhabitants of Korond (Corund, Romania).

Pottery craftsmanship dates back to about three centuries in the village according to the written records. Potters in Székelyudvarhely (Odorheiu Secuiesc, Romania) sued the craftsmen of Korond, because they had stolen the secrets of pottery from them. In the second half of the 18th century the Habsburg Court banned the use of lead in pottery, in Korond too, because lead was needed for warfare. So the fact that potters in Korond used lead-glaze can no doubt be traced back to about three centuries.

At present 440 families practice pottery in the village according to official records. During their work the glazing of pottery items is done with the help of lead-glaze. The raw lead-oxide solution mixed with kaolin is used for the glazing of crockery and other items. After that they bake pottery items glazed with raw glaze at about 900 °C. The steam emitted by and surrounding the furnace during this kilning process contains lead, which is inhaled by the people present. Near the furnace there is significant lead contamination, which has been proved by measurements at the work-site.

Children learn the craft from as early as the age of 6-7, so they are exposed to the effects of lead contamination early. This means that about 2200 inhabitants of the village are exposed to the direct effects of lead.

For the purpose of this study we examined 24 persons altogether: 12 adults and 12 children. We have shown the observed symptoms in Table 1. In addition to paleness we

observed a significant incidence of the symptoms indicative of vegetative disorders. We determined the blood count and the delta-aminolevulinic acid content of the urine before administering doses of the HUMET-R syrup (in accordance with the authority-modified Mauzerall-Granick method). When defining the methodology we considered 5mg/l delta-aminolevulinic acid level "increased", and we classified as "pathological" the level above 10 mg/l.

At the time of distributing the Humet-R samples we instructed the persons who were exposed to the effects of lead contamination to take one teaspoonful of the roborant preparation twice a day. After taking two weeks' dose of the preparation we repeated the determination of blood count and the delta-aminolevulinic acid level.

Results and evaluation

We presented numerical data in Tables 2 and 3. The results show that the blood counts of both at the adults and the children improved after the administration of the roborant preparation, in the first group it increased from 4,000,000 to mean values of 4,500,000, and in the children from 3,800,000 close to 4,000,000.

The results of delta-aminolevulinic acid determination show a more apparent improvement, it barely exceeded the 6 mg/l level as measured in adults compared to the mean baseline value of just above 9 mg/l, while the mean baseline value of above 10 mg/l in children decreased to about 7.5 mg/l.

THE INCIDENCE OF CLINICAL SYMPTOMS IN LEAD EXPOSURE

	data / %
disorders of sleep	20 / 83.3 %
disorders of the memory	18 / 75,0 %
increased dermographism	15/ 62.5 %
decreased muscular strength	16/ 66.6 %
headache	20/ 83.3 %
vertigo	19/ 79.2 %
visual disturbance	14/ 58.3 %
paleness	18/ 75.0 %
tremor	5/ 20.8 %
constipation	12/ 50.0 %
meteorism	11/ 45.8 %
muscular,-articular pains	10/ 41.60 %
nausea	5/ 20.8 %

DELTA-AMINOLEVULINIC ACID LEVEL mg/l

adults		children	
before treatment	after treatment	before treatment	after treatment
5.8	4.2	12.0	10.0
4.5	4.5	11.0	6.0
6.2	4.5	8.4	6.4
8.4	5.0	7.6	6.6
12.0	7.2	6.4	6.0
11.0	6.2	6.6	5.6
14.0	8.5	14.2	8.6
20.0	11.0	16.4	9.0
14.0	7.2	12.0	10.0
8.2	5.6	8.4	6.6
7.9	6.5	9.6	7.0
8.8	4.2	12.0	9.0
9.23	6.21	10.38	7.56

Adults		Children	
before treatment	after treatment	before treatment	after treatment
red blood cell count		red blood cell count	
3,900,000	4,120,000	3,840,000	4,120,000
3,920,000	4,000,000	3,960,000	4,000,000
4,000,000	4.120,000	4.120,000	4,200,000
4,100,000	4.200,000	4,000,000	4,200,000
4.000,000	4,400,000	3,820,000	4,120,000
3,940,000	4.100,000	3,940,000	4,120,000
4,120,000	4,120,000	3,800,000	4,000,000
4,200,000	4,400,000	3,760,000	4,000,000
4,180,000	4,200,000	3,800,000	4,200,000
4,000,000	4,200,000	3,960,000	4,240,000
4,000,000	4,400,000	3,600,000	3,920,000
3,840,000	4,120,000	3,840,000	3,960,000
4,016,666	4,541,666	3,870,000	4,090,000

The above results unanimously prove the beneficial effects of the HUMET-R syrup in people working in lead exposure. The improvement of the blood count can unquestionably be attributed to the macro and microelements of the roborant preparation, while the decrease of delta-aminolevulinic acid dejection which indicates disorders of the synthesis of tetrapirrol rings caused by lead can be explained by the complexon effect of the humic acid and the elements of the syrup.

CONCLUSION

The beneficial effect of HUMET-R syrup administered to persons working under lead exposure is justified after a two weeks' administration. This is evidenced by the improvement of the blood count, and the decrease of delta-aminolevulinic acid dejection, which is a factor indicating the damaging effects of lead.

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Effect of the Consumption of Humic Acid with Bound Complex Micro Elements in Cases of Occupational Cadmium Exposure

Humic Acid Bound Micro Elements in Cadmium Exposure

Key words: cadmium, occupational exposure, humic acid, micro-elements, health protection.

Aranka Hudák[‡] M. D. Ph. D., Miklós Náray D. Chem., Imre Nagy M. D., György Ungváry M. D., Ph. D., D. Sc.,

National Institute of Occupational Health, Budapest, P.O.Box 22, H-1450, Hungary.

Corresponding author: [‡]**Aranka Hudák** M.D. Ph.D.,
National Institute of Occupational Health, Nagyvárad tér 2. Budapest, H-1096.
Hungary. - Postal address: P.O.Box 22. H-1450 Budapest, Hungary.
Tel.: (361) 215 7890, Fax: (361) 215 6891.

Abbreviations:

ALAT: alanin aminotransferase,	ASAT: aspartate aminotransferase,
Cd-B: blood cadmium concentration,	Cd-U: urine cadmium concentration,
EQC: external quality control,	GGT: gamma glutamyl transferase,
HME: humic acid with bound microelements	
IQC: internal quality control,	NAG: N-acetyl-glucosaminidase,
SD: standard deviation	Cr. : creatinine

Abstract

Based on the metal chelating capacity of humic acid and the well-known interaction of cadmium with other micro/trace elements, this study was aimed at determining whether the daily consumption of humic acid with bound complex micro elements (HME) has beneficial effect in cadmium workers. Blood and urine cadmium concentrations (Cd-B and Cd-U), haematology, liver and kidney tests were measured in two groups of cadmium exposed workers (Group A: 9 persons working in alkaline battery production; Group B: 22 persons working in a metal plating workshop) before and after a six weeks treatment schedule. Cd-B was significantly decreased in group A from 47.73 to 27.24 $\mu\text{mol/l}$ and in group B from 8.55 to 7,17 $\mu\text{mol/l}$. Cd-U was increased significantly in group A from 3.21 to 4.25 nmol/mmol creatinine but not in group B. In most cases the initially abnormal serum iron levels and markers of liver and kidney function improved. Daily consumption of HME for six weeks seems to decrease uptake and increase urinary excretion of cadmium and to improve the iron status and other adverse laboratory changes found in the workers. Regular consumption of HME may contribute to health protection an effective means of prevention and in cases of occupational cadmium exposure.

Key words: cadmium, occupational exposure, humic acid, micro-elements, health protection.

INTRODUCTION

Cadmium is a potentially dangerous, toxic heavy metal of both environmental and occupational health concern mainly because of its extremely cumulative nature (Ahlgren et al., 1981; WHO, 1992). Its half-life clearance times in the organs and tissues may be several years, or even decades according to the literature (Kjellström and Nordberg, 1978; Wai-Yee and Rennert, 1988; WHO, 1992). Cadmium content of the organs gradually increases over the lifetime of the individual (Anke and Schneider, 1974; Elinder et al., 1976; Kowal et al., 1979; Travis and Haddock, 1980; Ellis et al., 1981; Chung et al., 1986; Svantengren et al., 1986). A number of experiments prove that absorption of cadmium from the gastrointestinal tract and its toxicity are influenced by the supply of micro- and trace elements (Zn, Cu, Fe, Se, Ca), the absorption of which is adversely affected by the presence of cadmium, while food supplemented with micro/trace elements may decrease cadmium absorption and alleviate toxicity (Hamilton and Valberg, 1974; Magos, 1976; Parizek, 1976; Flanagan et al., 1978; Fox, 1979; WHO, 1992). Literature data also proves that a component of natural peat, humic acid, is capable of chelating metal ions (Zajka, 1995; Kőhegyi, 1995) and in chicks its administration with cadmium decreased the absorption and accumulation of the latter (Herzig et al., 1994).

The aim of this study was to examine whether daily consumption of a humic acid based complex micro/trace element preparation (HME) (Zajka, 1995; Kőhegyi, 1995) over a period of six weeks can decrease the absorption or

increase the excretion of cadmium and have a beneficial effect on the adverse clinical laboratory changes attributable, at least partly, to cadmium exposure.

METHODS

Two groups of workers participated voluntarily in the study, after being informed of the purpose, duration, and expected benefit of the treatment. Group A consisted of 7 male and 2 female workers employed in alkaline battery production (Plant A), while Group B comprised of 18 males and 4 females working in a metal plating factory (Plant B). Some characteristics of the subjects are shown in Table 1. All subjects were symptom-free, had no complaints and were fit to work during the entire study period. The first set of tests was carried out as part of the annual periodic medical examination. Following this the subjects consumed daily 10 ml of HME for six weeks. At the end of the treatment period all laboratory tests were repeated.

Table 1. Distribution of cadmium workers according to plant, sex, smoking habit, age and exposure time (mean \pm SD; range)

	Plant A (alkaline battery production)				Plant B (metal plating)			
	males		females		males		females	
	smokers	non-smokers	smokers	non-smokers	smokers	non-smokers	smokers	non-smokers
n =	4	3	2	0	3	15	2	2
age (years)	45,4 \pm 8,2 33 - 59		50,0 \pm 0 50 - 50		39,7 \pm 10,4 23 - 70		54,0 \pm 4,8 49 - 59	
Exposure time (years)	8,8 \pm 6,1 1,5 - 17		12,0 \pm 1,4 11 - 13		8,3 \pm 5,0 1 - 20		11,0 \pm 1,2 10 - 12	

HME (Humet[®]-R syrup - HORIZON-MULTIPLAN) contains 10 elements of vital importance bound to a colloidal solution of humic acids (natural bio-polymers, component of peat) in chelat form. The amounts contained in a 10 ml dose (potassium: 36,7 mg, magnesium: 15 mg, iron: 14 mg, zinc:10 mg, manganese: 3 mg, copper: 2 mg, vanadium: 0,5 mg, cobalt: 0,2 mg, molybdenum: 0,175 mg, selenium: 0,125 mg) of HME, do not exceed the respective recommended daily intake for any elemen (WHO, 1992; Zajka, 1995; Kőhegyi, 1995).

Blood and spot urine samples were taken in the morning. Venous blood samples were drawn from the antecubital vein using Becton Dickinson tubes, and urine samples were collected into polyethylene containers previously washed with acid.

Biological exposure indices: blood and urine cadmium concentrations (Cd-B, Cd-U) (Lauwerys et al., 1979; Vahter, 1982; Ghezzi et al., 1995) were measured with Zeeman background correction graphite furnace atomic absorption spectrometry (urine samples were diluted, blood samples were deproteinised). For internal quality control (IQC): Seronorm Whole Blood I-II and Seronorm Urine (Nycomed AS Norway) were used. External quality assurance (EQC) was relied on UK NEQAS. Complete blood cell count was determined by MS8, a 18 parameter Haematological analyser (Melet-Schloesing, France). For IQC 3 levels of CBC-8 control blood (R&D system inc.) were used. Serum aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) and gamma-

glutamyl transferase (GGT) activities, serum urea, creatinine, uric acid, iron concentrations and total iron binding capacity, urine protein and creatinine concentrations were estimated with AL Plus clinical chemistry analyser and AL Instruments Ltd test kits. For IQC: Elextrol N and P control sera (AL Instruments Ltd) were used. EQC for haematology and clinical chemistry was relied on ÖQUASTA, Austria. Urinalysis was performed using BIOSCAN test stripes. Urine N-acetyl- β -D-glucosaminidase (NAG) activity was measured with colorimetric method adapted to AL Plus analyser (Kiss et al., 1996). Urine parameters were corrected for creatinine (Cr.) concentration.

Statistical analysis was performed using SPSS for MS Windows version 6.1. Arithmetic means and SD were calculated. Paired t-test was used for comparison of the means of the parameters before and after treatment.

RESULTS

The initial mean Cd-B and Cd-U of the subjects depended on the workplace and on their smoking habit (Lewis et al., 1972; Vahter, 1982; Elinder et al., 1983) (Table 2). In Group B (metal plating factory) smokers' (n=17) mean Cd-B and Cd-U was double that of non-smokers. In Group A (alkaline battery plant) smokers (n=5) had four fold higher mean Cd-B and Cd-U, than non smokers (n=3). In Group A values of one subject (No 110, a smoking male) were excluded from the group means, because his Cd-B and Cd-U exceeded the limit values for these exposure indices allowable in Hungary (90 nmol/l for Cb-B and

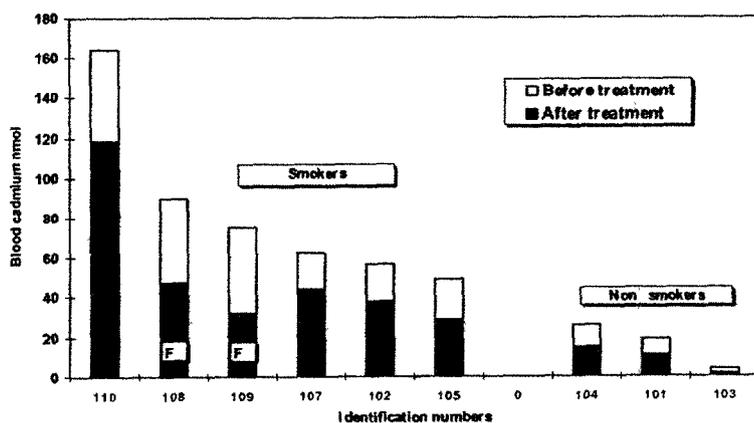
10 nmol/mmol creat for Cd-U) and he had signs of tubular dysfunction (low serum uric acid and high urinary protein concentration and NAG activity).

Table 2. Changes of Cd-B (nmol/l) and Cd-U (nmol/mmol Cr.) on the effect of six-week humic acid - micro element consumption in cadmium workers (males, females together)

		Before treatment		After treatment		p<
		Mean±SD	Range	Mean±SD	Range	
Plant A						
non-smokers	Cd-B	16,30±11,3 6	3,80 - 26,0	9,18±6,98	1,52 - 15,19	NS
n=3	Cd-U	1,09±0,25	0,81 - 1,15	1,69±0,65	0,99 - 2,27	NS
smokers	Cd-B	66,58±16,0 4	36,50 - 89,7	38,07±7,77	28,86 - 47,56	0,01
n=5	Cd-U	4,54±3,08	2,57 - 9,95	5,79±2,97	3,37 - 10,74	0,05
All	Cd-B	47,73±29,4 3	3,80 - 89,70	27,24±16,4 9	1,52 - 47,56	0,01
n=8	Cd-U	3,21±2,97	0,81 - 9,95	4,25±3,11	0,99 - 10,74	0,02
Plant B						
non-smokers	Cd-B	6,93±3,90	2,25 - 16,12	5,69±3,45	1,79 - 13,93	0,01
n=17	Cd-U	1,03±0,60	0,30 - 2,60	1,34±0,77	0,41 - 2,75	0,05
smokers	Cd-B	14,07±6,79	7,60 - 23,33	12,21±5,0	7,03 - 18,36	NS
n=5	Cd-U	2,06±1,38	0,50 - 3,73	1,49±0,78	0,54 - 3,63	NS
All	Cd-B	8,55±5,46	2,25 - 23,3	7,17±4,65	1,79 - 18,36	0,00 1
n=22	Cd-U	1,26±0,91	0,30 - 3,73	1,44±0,88	0,41 - 3,63	NS

Following the six-week consumption of HME the mean Cd-B decreased significantly in both groups (Table 2, Figs. 1, 2). The decrease was especially marked - nearly 50 % - in Group A. When smokers and non-smokers of both groups were evaluated separately, the decrease was not significant in the case of

Group A non-smokers (n=3) and Group B smokers (n=5) owing to the small number of subjects. For Cd-U, there was a significant increase in Group A as a whole, and in smokers alone (except No 110, whose Cd-U decreased from 44.8



to 38 nmol/mmol Cr.), and in non-smokers of Group B (Table 2, Fig. 3).

Figure 1. Decrease of blood cadmium concentration in Group A workers (alkaline battery plant) on the effect of consumption of humic acid - micro element preparation for six weeks. F: female.

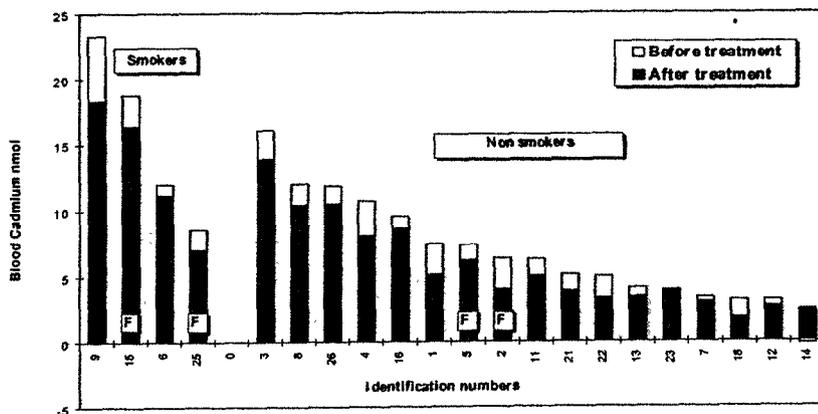


Figure 2 Changes of blood cadmium concentration in Group B workers (metal plating factory) on the effect of consumption of humic acid - micro element preparation for six weeks. F: female.

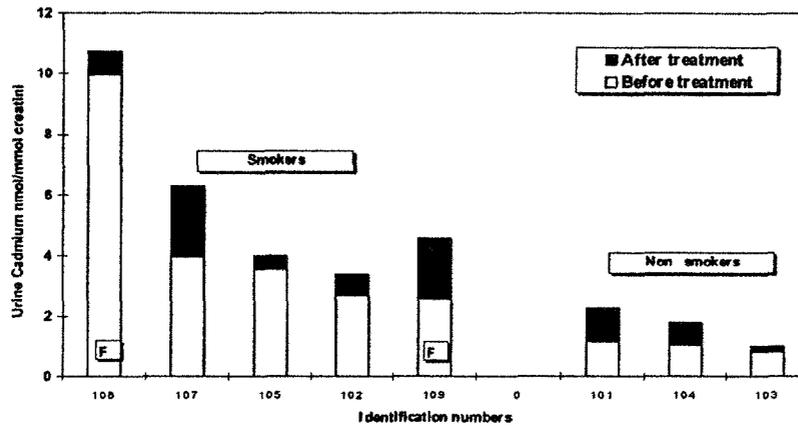


Figure 3. Increase of urine cadmium concentration in Group A workers (alkaline battery plant - except No 110) on the effect of consumption of a humic acid - micro element preparation for six weeks. F: female.

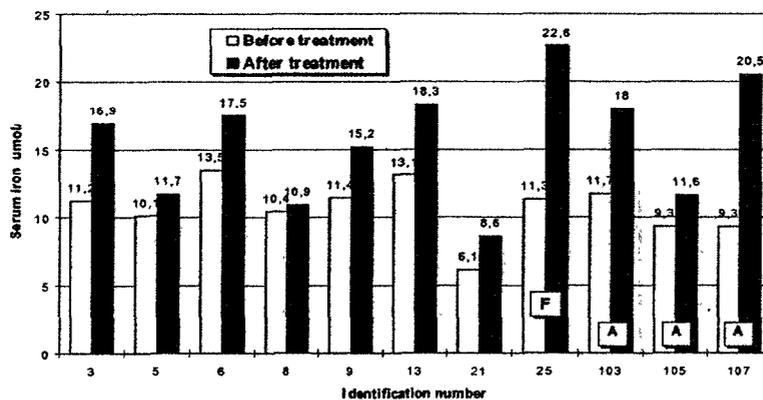


Figure 4. Increase of serum iron concentration in cadmium exposed workers with initial sideropenia on the effect of consumption of humic acid - micro element preparation for six weeks. A: Group A; F: female.

Before treatment serum iron concentration was found lower than normal (<14 $\mu\text{mol/l}$ in males and <12,5 $\mu\text{mol/l}$ in females) in altogether 11 persons out of 31 (10 males and 1 female). As a result of the six-week HME consumption serum iron level improved in all cases but one (Fig. 4).

Table 3. Changes of some clinical laboratory parameters on the effect of six-week humic acid - micro element consumption in cadmium workers

	Laboratory parameters	Before treatment		After treatment		p<
		Mean \pm SD	Range	Mean \pm SD	Range	
Plant A						
males n=6*	Urine protein mg/mmol Cr.	5,85 \pm 2,23	2,70 - 8,9	3,33 \pm 0,87	1,9 - 6,2	0,01
Plant B						
males n=18	Serum ALAT U/l	46,7 \pm 34,3	13 - 153	37,6 \pm 25,6	13 - 105	0,02
	Serum GGT U/l	63,3 \pm 86,7	15 - 396	51,7 \pm 58	11 - 261	NS
	Uric acid $\mu\text{mol/l}$	423 \pm 107	221 - 587	333 \pm 110	180 - 644	0,001
	Urine protein mg/mmol Cr.	9,76 \pm 16,7	2,3 - 74,2	5,45 \pm 11,8	0,45 - 52,2	0,01
females n=4	Serum ALAT U/l	30,5 \pm 24,4	17 - 67	21,5 \pm 9,1	17 - 35	NS
	Serum GGT U/l	37,3 \pm 26,1	22 - 67	28,5 \pm 18,6	10 - 52	NS
	Uric acid $\mu\text{mol/l}$	248 \pm 69	172 - 334	201 \pm 27	183 - 241	NS
	Urine protein mg/mmol Cr.	15,2 \pm 19,9	4,1 - 45	5,0 \pm 3,6	2,9 - 10,5	NS

The mean activity of ALAT decreased significantly, while that of GGT showed a decreasing tendency in Group B males (Table 3). Five of the 7 persons with

ALAT and GGT values higher than normal, showed improvement. The initial mean serum uric acid concentration was higher in Group B males, than in group A males (423 ± 107 and 311 ± 53 $\mu\text{mol/l}$, respectively) and it decreased significantly after the treatment (Table 3). Seven of the 8 males with higher than normal values (>420 $\mu\text{mol/l}$) showed decrease (Fig. 5). The mean urine total protein concentration decreased in both groups (Table 3). The abnormally low serum uric acid and urine total protein concentrations in subject No 110 did not change.

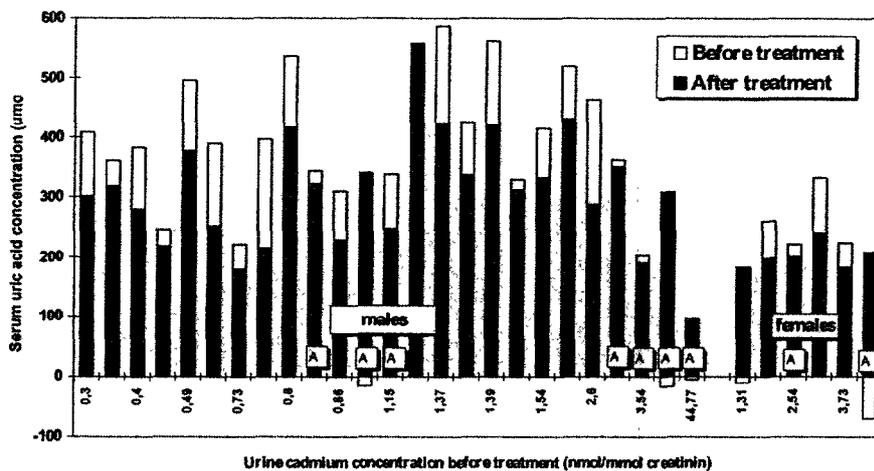


Figure 5. Changes of serum uric acid concentration in cadmium exposed workers on the effect of consumption of humic acid - micro element preparation for six weeks. A: Group A; F: female.

Group B females showed similar changes in ALAT, GGT and uric acid, but these were statistically non-significant due to the small number of subjects (Table 3).

The mean values of the haematologic parameters, serum bilirubine, creatinine and urea did not change in any of the groups.

No adverse effect or complaint attributable to the treatment was observed during the study period and no discontinuation became necessary in any of the cases.

DISCUSSION

Data from a number of experiments proves that nutritional factors may influence cadmium absorption and toxicity (Hamilton and Valberg, 1974; Magos, 1976; Parizek, 1976; Flanagan et al., 1978; Fox, 1979; WHO, 1992; Vahter et al., 1996). Flanagan et al. proved in animal experiments that sideropenia increased the absorption of cadmium, and in human studies, they found an inverse relationship between absorption of cadmium and serum ferritin level. They attributed the higher rate of cadmium absorption in women to their deficient iron stores. The most recent data from Vahter (1996) also stresses that cadmium absorption is inversely related to serum ferritin concentration in women. The low protein, calcium, selenium, zinc and copper content of food consumed increases, while excess of zinc, iron, selenium decreases cadmium absorption and toxicity (Sanstead, 1976; WHO, 1992). At the same time, cadmium inhibits the absorption of trace elements, causing deficiency or aggravating an existing deficiency (WHO, 1973, 1992). Appearance of the signs of deficiency can be prevented by supplementing trace elements (Fox, 1978; WHO, 1992).

HME, administered in our study, may act like an ion exchanger in the gastrointestinal tract, freeing trace elements bound with varying force in chelate form, and binding other elements present there, such as cadmium (Zajka, 1995; Kőhegyi, 1995). Based on the above, regular consumption of HME was expected to decrease cadmium uptake from the gastrointestinal tract, which may be considerable in workers - especially in smokers - owing to hand-mouth movements during work.

Following the consumption of HME over a period of six-weeks, the mean Cd-B significantly decreased in both groups, despite continuing exposure. The higher the initial Cd-B, the greater the decrease that was measured (Figs. 1,2). The decrease can be attributed first of all to the inhibition of cadmium uptake from the gut, directly by the humic acid component (Herzig et al.,1994) and indirectly by the micro-element supplement. Increase of urinary cadmium excretion may also play a role. Cd-U increased significantly in individuals of Group A (Fig. 3) - except subject No 110 with very high Cd-U values and frank proteinuria - and in Group B non-smokers (Table 2). Also among Group B smokers there were 2 persons with proteinuria in whom Cd-U decreased, similarly to subject No 110. It seems that only persons without proteinuria responded to HME with an increase of Cd-U. The mechanism of the increase of Cd-U, however, needs further investigation.

Among the liver function tests, activities of ALAT and GGT were elevated in several cases in Group B. Cadmium is not considered hepatotoxic in humans, although increased activity of hepatic enzymes was observed in monkeys as a result of cadmium treatment (WHO, 1992). As anamnesis and other test results did not support alcoholic origin, it was assumed that cadmium exposure may be partly responsible for the elevated enzyme activities, which may represent adaptive changes. This can be explained by the fact that liver cells participate in storing cadmium and synthesise metallothionein, the transport protein for cadmium (Kjellström and Nordberg, 1978; Chung et al., 1986; Koropatnick and Cherian, 1988;WHO, 1992).

As for renal function tests, an interesting finding was the elevated serum uric acid level before treatment in Group B - but not in Group A - which significantly decreased as a result of HME consumption (Fig. 5). In the literature we did not find data on high serum uric acid level caused by cadmium, perhaps because usually populations with greater cadmium exposure were studied - like our Group A - with already slightly impaired tubular reabsorption capacity, resulting in uricosuria (later also aminoaciduria, proteinuria) and consequently lower serum uric acid level (Schroeder and Balassa, 1961; Wai-Yee and Rennert, 1988; WHO, 1992). When renal tubular function is intact, uric acid filtrated in the glomeruli is completely reabsorbed by the tubuli and the amount of uric acid appearing in the final urine is the result of active tubular secretion (Henry, 1969). Our results may indicate that altered renal handling of uric acid due to the impairment of tubular secretion may be an early sign of the renal effect of cadmium which seems reversible, unlike to the irreversible tubular nephropathy, appearing later and presenting with uricosuria, together with aminoaciduria, proteinuria, due to the impairment of tubular reabsorption (Friberg, 1948; Schroeder and Balassa, 1961; Falck et al., 1983; Mason and Davison, 1988; Wai-Yee and Rennert, 1988; Roels et al., 1989; WHO, 1992). Alcoholic origin of the elevated serum uric acid level (Watson, 1986) could not be supported. Increased NAG activity, a well-known sign of cadmium induced renal tubular damage (Bernard et al., 1979; Meyer and Fischbein, 1984; Jarup et al., 1995) was present in both groups and did not change significantly as a result of the treatment.

It is also important to note, that low iron level cases, which were conspicuously more frequent than usual among males, improved during the six-week HME treatment.

We assume that the improvement of the liver and kidney function markers is not attributable to the decrease of Cd-B, as organ cadmium levels probably did not change considerably during the relatively short treatment period, (bearing in mind the long half-life of cadmium in the body), but rather to the direct effect of the preparation on the micro-element status and balance in the body, which plays an important role in the optimal functioning of a number of different enzymes (Fox, 1979; WHO, 1992).

In summary, daily consumption of HME for six weeks decreased Cd-B and increased Cd-U in workers continuously exposed to cadmium. Thus HME seemed to decrease the uptake and increase the urinary excretion of cadmium. In addition, it improved the iron status and the other adverse laboratory changes detected. Consumption of HME may be an effective means of health protection and may contribute to prevention of adverse health effects in occupational cadmium exposure.

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LEGENDS

- Figure 1 Decrease of blood cadmium concentration in Group A workers (alkaline battery plant) on the effect of consumption of humic acid - micro element preparation for six weeks. F: female.
- Figure 2 Changes of blood cadmium concentration in Group B workers (metal plating factory) on the effect of consumption of humic acid - micro element preparation for six weeks. F: female.
- Figure 3 Increase of urine cadmium concentration in Group A workers (alkaline battery plant - except No 110) on the effect of consumption of a humic acid - micro element preparation for six weeks. F: female.
- Figure 4 Increase of serum iron concentration in cadmium exposed workers with initial sideropenia on the effect of consumption of humic acid - micro element preparation for six weeks. A: Group A; F: female.
- Figure 5 Changes of serum uric acid concentration in cadmium exposed workers on the effect of consumption of humic acid - micro element preparation for six weeks. A: Group A; F: female.

HUMET Trade, Research and Development Co.
1121 Budapest, Konkoly Thege u. 29-33.



**Retrospective evaluation of the data
of patients treated with humic acid metal complex
(case reports)**

Elek Csucska Vet.D.

1991

Case reports of patients suffering from cancer treated with a preparation called "HUMET" /formerly called "humo chelate"

1./ Mrs. T. Sz., resident of Keszthely, aged 78

In the summer of 1969 she was hospitalised for examination on the account of complaints that she had had for some time, which turned suddenly severe.

Complaints: in 2 months she lost 15 kg in weight, she had strong abdominal pains accompanied with grave intestinal haemorrhage, and she got completely weakened physically.

In the Surgical Section of the Zalaegerszeg Hospital she was diagnosed to have a tumour of the size of a green walnut in the rectum at about 15 cm from the anus. The histological feature proved to be adenocarcinoma. The only possible treatment recommended was urgent radical operation, and it was stressed that a delay of even one month could be fatal.

The patient rejected preternatural anus as a surgical solution, she did not agree to it.

The patient turned to me saying she would not have the operation. She was prepared to die, but she would be willing to try the preparation on her own risk. I pointed out to her that her decision meant assuming fatal risks, but as I could not get her to agree to the operation I started giving her the preparation on a regular basis.

Her physical state started to improve quickly, and she regained her bodyweight, her abdominal pains and intestinal haemorrhage stopped soon. In half a year all her pathological symptoms ceased.

She never received irradiation therapy or cytostatic treatment.

To date she has survived her disastrous condition of 1969 by 22 years.

2./ Dr. L. J., resident of Keszthely

Was operated for tumour of the colon in February 1978. The operation included excision of the intestine together with preternatural anus. The histological feature was adenocarcinoma. The wife of the patient was told to prepare for the worst.

The wife turned to me and asked me to provide her husband with the preparation regularly. He took the substance continually for 1 year and then in treatments of three times annually.

The patient's condition improved fast, so that in September 1978 his preternatural anus was stopped by restitution operation.

The patient never received irradiation therapy or cytostatic treatment.

The patient died at the age of 82 in 1989.

Cause of death: multiple sclerosis + Parkinson's disease.

3./ L. V., resident of Szóc, aged 67

Was admitted to hospital for examination in July 1983, with suspected tumour of the colon. Diagnosed in the course of exploration as:

"Tu. coli descendensis in stad. incur. 153.2"

(i.e. incurable tumour of descendent colon),

at the same time preternatural anus was performed.

Wife told that patient was past recovery and would die soon.

Patient's wife turned to me at this point. I supplied the preparation continually for 1 year, and even after that the patient underwent 2-3 treatments annually.

Patient improved fast and got strengthened.

In May 1985 restitution operation was performed in Surgical Clinic No. II. of the Medical University, Budapest.

The patient has been asymptomatic and healthy ever since.

The patient never received irradiation therapy or cytostatic treatment.

4./ Mrs. F. G., resident of Budapest, aged 61

Operated for breast cancer in August 1986, and one breast was removed. Because of metastasis found in regional lymph nodes that had been removed during drastic operation an unfavourable prognosis was made.

I was contacted and requested to administer the preparation as a regular treatment. The patient has taken the substance regularly to this day since early October 1986.

She never underwent cytostatic therapy. She is now asymptomatic and healthy. Her husband is a head physician, who is willing to witness.

5./ Dr. J. Gy., resident of Balatonfüred

Operated for extensive colonal adenocarcinoma of advanced stage on December 4, 1986. Intestine of approx. 60 cm had to be removed.

Received no cytostatic therapy.

Has taken the preparation regularly since February 5, 1987.

Feels well, asymptomatic.

As a retired head physician, he is willing to give testimony regarding the treatment.

6./ Mrs. L. Z., resident of Budapest

Diagnosed to suffer from tubal cancer or "Neopl. tubae". Her uterus together with the appendage was removed by the end of 1983.

Later the tumour relapsed. In February 1988 tumours of the size of green walnut and egg were found in the vaginal stump. In October tissue hyperplasia was found along the postoperative scar of the lower abdominal wall also. In a truly heroic struggle for the life of the patient, repeated irradiation and cytostatic therapies were carried out. In the meanwhile preternatural anus was also performed, and the ureters were also connected to the intestines through a rectovaginal fistula.

In early 1990 the husband was told to get prepared for the death of his wife as all treatments were in vain.

Responding to the aggressive demand of the husband I have administered the preparation since early March, 1990.

The patient has recovered from critical state and - given the existence of a person suffering from all the consequences of these operations - she now feels well. Her physical condition has improved, she has become strengthened. She gets up from bed during the day and does some housework.

Of course one cannot say she has been cured or healed, but she is alive.

7./ Mrs. T. K. M., resident of Székesfehérvár

Once operated for erosion of cervical orifice, but this relapsed in early 1990. She requested the preparation by the end of June. She had normal laboratory findings by November.

8./ Mrs. B. K.

Exploratory laparotomy in April 1984 showed that the surroundings of the cardia and the liver itself were indurated by tumour and the surface of peritoneum was also disseminated. She was declared inoperable and sent home with the prognosis of death in the near future.

Her son who lives in Pápa - he has died since - visited me and asked me to help as a last resort. The patient took the preparation regularly for 6 months. Soon she gained 13 kilograms in weight and got strengthened physically. Her working ability returned. She did have recurring abdominal pains though /adhesion?/.

This year I heard from her grandson that disregarding her brain sclerosis of advanced stage- a consequence of her old age - she feels fine and her tumour has not recurred.

9./ Dr. Mrs. K. G., resident of Keszthely, aged 66.

Operated for malignant tumour of the uterus in August 1975, her uterus together with the appendage was removed.

Histopathologic diagnosis:

"Adenoma malignum endometrii..."

(e.g. malignant adenocarcinoma in the endometrium)

Following the operation she asked the humo-chelate preparation from Dr. Elek Csucska to prevent dissemination of tumour or relapse.

She has taken the preparation as a treatment ever since, but no longer because of cancer phobia, but for regeneration and roboration.

She received no cytostatic or other oncological treatment.

She is in perfect health condition now.

10./ L. Sch., resident of Budapest, aged 56.

Operated because of the risk of ileus on December 18, 1989. The obstruction had been caused by the ascendent tumour of the colon that propagated onto the liver as well. The histological feature was metastasis in the mesenteric lymph nodes.

Official diagnosis:

"Tu. colonis ascendentis propag. ad cholecystam-met.
Lymphoglandularum meseterii."

(i.e. Tumour of the colon propagated to the cholecysta and metastasis on mesenteric lymph nodes)

Son told that patient would die soon /in 1-2 months/ of inoperable carcinoma.

The patient received no cytostatic therapy.

On March 10, 1990 the patient and family visited me. He was in a very bad condition. He would try taking the preparation as a last resort.

The completely weakened, skin-and-bone patient, who was under stress because of fear of death, gained strength following the starting of treatment and is now able to work. However he is still nervous.

CT examination carried out on February 15, 1991 did not show traces of relapse in the operated section. What is more, the enlargement of mesenteric lymph nodes that had been discovered earlier when operated, could not be detected.

Documents of the above cases are fully available.

Keszthely, July 15, 1991.

Dr. Elek Csucska

Keszthely, Bercsényi u. 62.

**Hungarian State Railway
Public Health Institute
H-1068 Budapest, Dózsa Gy. U. 112.**

HUM 031

**The Study of HUMET-R syrup's Effect on the Metabolism of Trace
Elements in Healthy Volunteers**

Dr. Molnár Miklós

1992.

The Study of HUMET®-R Syrup's Effect on the Metabolism of Trace Elements in Healthy Volunteers

1. Introduction

Micro-elements function as components of enzyme structures and often as their activators. The lack of micro-elements or the dominance of their antagonists has an adverse effect on the functioning of the enzymes and may thus lead to deficiency syndromes of symptoms signaling pathological enzyme activities.

The body's micro-element need is satisfied by varied nutrition with normal absorption. However, the micro-element content of our nourishment has changed both quantitatively and qualitatively. Micro-elements are not present in sufficient quantities in the soil and, therefore, in vegetables or meats. The problem is further complicated by the fact that even a sufficient amount of micro-element intake cannot be absorbed. For that reason the general trend is to ensure an appropriate quantity and quality of trace element input regularly and independent of one's diet.

The accumulation of heavy metals in the body has increasing importance both from occupational and environmental health perspectives. Cadmium is an important component of plastic, paint, pesticide and battery production. Cadmium gets into our bodies through vegetables and fruits, because of soil pollution, from foodstuff in contact with plastic instruments or packaging materials and through cigarette smoke. Accumulated in the kidney it has harmful effects, hinders the functioning of enzymes that contain zinc. It destroys the calcium-phosphorus balance, which in turn leads to osteoporosis. In animal tests it proves to be teratogenic and carcinogenic (lung cancer). It has an adverse effect on the utilization and incorporation of iron, causing iron deficiency anemia. This pathological state can be overcome by

administering an appropriate quantity of iron, with the right chemical bondage, zinc and copper together.

Lead poisoning appears as an occupational hazard in the case of numerous work processes: paint, battery or lead pipe manufacturing or printing. Even those who are not endangered from an occupational point of view are exposed to lead from industrial sites, transportation, urbanization and adulterated foodstuff. Lead inhibits hemoglobin generation and decreases nerve fibers' transmission capabilities. Lead's orchilytic and sterilizing effect has long been known. It accumulates in the bones, the kidney and the liver and is discharged from these spots ensuring a stable blood-lead level. Iron and lead compete with each other: thus, with the administration of appropriate amounts of iron the risk of lead poisoning can be decreased. The administration of zinc has a similarly favorable effect.

The base of HUMET[®]-R Syrup, a colloid solution containing a mixture of humic acids, is an optimal carrying agent. Because of its variable functional groups:

- it contains the trace elements in a biochemical structure, chelate bonding, which is similar to that of the organism's transport-proteins, so it is easily absorbed;
- it contains macro and micro elements (potassium, magnesium, iron, zinc, manganese, copper, vanadium, cobalt, molybdenum and selenium) corresponding to the internationally recommended daily amount (RDA) and releases these metals by way of a dynamic chelate bonding mechanism matching the body's needs;
- undesirable, frequently harmful elements, e.g. lead or cadmium, are removed from the body as a result of their strong bondage with humic acids.

The micro element transmittal of HUMET[®]-R is accomplished through the enzymes of the intestine's wall. These micro-elements bond with albumin, transferrin and metallotionein. The heavy metals discharged with bile and intestinal secretion are bonded by the released chelate

capacity in the intestinal tract, thereby blocking re-absorption. The heavy metal-chelate complexes leave the body enterally.

2. The Study's Objective

In the course of the clinical study we have analyzed the effects of HUMET[®]-R syrup, which contains chelate forming humic acids and trace elements, on mineral metabolism in healthy volunteers in a relatively short, fourteen day, period of treatment.

HUMET[®]-R is believed to have a double effect: on the one hand, it speeds up the discharge of the accumulated harmful minerals from the body; on the other hand, it supplants the necessary trace elements. In our study we wished to evaluate the results of both processes with respect to some minerals and trace elements.

Questions:

1. Does HUMET[®]-R have an influence on hematopoiesis and iron metabolism?
2. What is the effect of the tested product on general laboratory parameters?
3. Does it help to clear minerals like lead and cadmium from the body? These minerals are harmful when substantial quantities are accumulated.
4. Does it efficiently raise the level of certain selected trace elements, like zinc and copper, in the blood?
5. Does the efficiency of the tested product depend on the body's exposure to certain heavy metals (cadmium and lead)?

3. Study Location

The examinations were carried out in the Hungarian State Railway's Public Health Institution.

General laboratory determinations were done in its Occupational Health Laboratory, specific determinations were carried out in the Central Laboratory of the Hungarian State Railway's Hospital and the Enzyme Diagnostic Laboratory of the Central Laboratory of the Hungarian State Railway's Hospital.

4. The Study's Population and Methods

4.1. The Study's Population

Fifty-one persons, both men and women, participated in the study. The age of the volunteers was between eighteen and sixty years.

The descriptive statistical data of the studied population can be found in Table I.

4.2. The Study's Methods

The volunteers appeared for examination at the Occupational Health Laboratory of the Hungarian State Railways, where a decision was made about the acceptance or rejection of applicants on the basis of physical status, blood pressure, pulse, general laboratory tests and EKG

Organic diseases requiring treatment with drugs or producing significant discrepancies in laboratory results and alcohol abuse were among the exclusion criteria

Before and after the fourteen day HUMET[®]-R treatment blood samples were taken in the laboratory. The following parameters were determined (unit of measurement in square brackets following the parameter's denomination):

- blood count: hematocrit [l/l], hemoglobin [g/dl], leukocyte count [l/mm³]; enzymes: SGOT [IU/l], GGT [IU/l], ALP [IU/l]; ions: Na [mmol/l], K [mmol/l], Ca [mmol/l], P [mmol/l];
- iron metabolism: serum iron [μmol/l], ferritin [μmol/l], TVK [μmol/l]; lead metabolism: blood-lead [μmol/l], urine lead [μmol/l], DALA-dehydrogenase [U/l], urine ALA [μmol/l]; copper metabolism: serum copper [μmol/l], blue plasmin [mg/dl]; serum zinc [μmol/l]; blood cadmium [μmol/l], urine cadmium [μmol/l].

The parameters listed in the first group were determined for information purposes primarily to exclude organ damaging side effects. With the statistical analysis of the parameters in the second group we intended to find answers to the questions mentioned in the introduction.

20 ml HUMET[®]-R syrup was administered once a day. In order to exclude interaction with food the volunteers took the tested product with 200 ml fruit nectar free of preservatives three hours after lunch.

Side effects were determined by questioning following the treatment.

4.3. The Methods of Evaluation

The statistical evaluation of the results was accomplished by calculating descriptive statistical parameters and hypothesis testing.

In the course of hypothesis testing pre- and post-treatment data were compared in single sample T-tests.

Groups were created within the studied population and the single sample T-test was repeated this way also.

- blood-lead level: $\geq 1.00 \mu\text{mol/l}$ (regarded as exposition),
- blood cadmium level: $\geq 0.08 \mu\text{mol/l}$ (regarded as exposition).

No significant overlapping was found among groups exposed to heavy metals, only in case of a single person did we find both high lead and cadmium levels.

We chose $\alpha=0.05$ as the significance level.

5. Results

The descriptive statistical results of the studied parameters can be found in Table 2.

Remark: due to technical reasons not each and every tested parameter was determined to be appropriate for each participant (rural screenings).

According to the T-test of the pre- and post-treatment laboratory parameters of the whole population the increase of full iron bonding capacity and serum copper level and the decrease of the cadmium level in the blood were significant. The summary of the results of hypothesis testing can be found in Table 3.

There was no significant change in the hemoglobin and hematocrit values ($<2\%$), the increase of TVK hardly reaches 5% which, in spite of its mathematical significance, cannot be regarded as significant from a clinical point of view. The 13.5% decrease of the ferrite level and the 9% increase of serum iron level are significant. Erythrocyte and iron metabolism values remained within normal laboratory ranges.

The decrease of the blood's cadmium level was significant from both statistical and biological perspectives ($p < 0.02$, a 73.2% decrease). The amount of cadmium in the urine decreased by 14.1%

The level of blue plasmin increased by 11%, which is mathematically insignificant. The serum copper level increased by 17.6%

The blood's zinc level did not change during the treatment (+0.7%).

Several parameters of lead metabolism changed considerably: the blood's lead level decreased by 10.7%, the amount of lead discharged in the urine increased by 17.6%, while ALA's activity measured in the urine decreased by 13.5%. The activity of DALA dehydrogenase remained unchanged (-1.2%).

The change in the general chemical parameters of the blood is insignificant, merely a few percentage points, except for GGT enzyme activity, which increased by 11.4% following the treatment, although in spite of the increase this was still well below the upper limit.

The single sample T-test was repeated for several relevant parameters among those exposed to cadmium (blood cadmium level $\geq 0.08 \mu\text{mol/l}$).

The parameters of hematopoiesis did not improve considerably. The average initial values of the cadmium exposed group were lower than the complete group's average hemoglobin level, the increase hardly reaches 2%. The situation is similar in case of hematocrit.

The parameters of iron metabolism were favorably affected by the treatment in this group: although the increase of serum ferritin does not exceed 4%, the increase of serum iron is almost 25%. Full iron bonding capacity increased by 3%.

The decrease of the blood's cadmium level ($p < 0.007$, an almost 90 % decrease) was convincing both from statistical and biological points of view. The amount of cadmium discharged decreased considerably (by 43%) in the urine during the treatment.

The level of free copper showed a small, 3.5% decrease. The increase of the blue plasmin level was 9%. Serum calcium remained unchanged during the treatment, while the increase of organic phosphorus did not reach 3% (see Table 4)

The single sample pre- and post-treatment T-test revealed a significant, 50%, decrease in the blood's lead level among those with initially high blood lead level ($1.00 \mu\text{mol/l}$)

We noted a small decrease in hematopoiesis: while the hemoglobin level practically remained unchanged, the hematocrit level decreased slightly (2.6%). The decrease of the ferritin level was 5.7%. Serum iron and TVK did not increase considerably (3% and 1.7%, respectively).

The increase in the activity of DALA-dehydrogenase is insignificant (1.2%) and the level of ALA measurable in the urine decreased by 18.6% during the treatment. The amount of lead discharged in the urine grew by 5.3% (see Table 5.).

The volunteers reported the following side effects: some abdominal pressure, nausea and softer feces.

6. Discussion

HUMET[®]-R efficiently decreased the blood levels of heavy metals in healthy volunteers during the two week treatment. In the population of fifty-one volunteers, fourteen persons had high cadmium levels in their blood (0.08 $\mu\text{mol/l}$) and eleven persons had high blood lead levels (1.00 $\mu\text{mol/l}$). We did not find significant overlapping among groups exposed to heavy metals, except for a single person who had both high lead and cadmium levels.

HUMET[®]-R decreased the blood's cadmium level significantly, by 73.2% ($p < 0.002$) with respect to the whole population. The decrease was also highly significant, 89.5%, in case of those exposed to cadmium. The overall decrease of the lead level was 10.7% for the general population, which was, however, statistically insignificant. Among those with high lead levels in the blood the decrease was 50.1% ($p < 0.002$).

The level of cadmium discharge in the urine also decreased following the treatment, which corresponds to the gastrointestinal heavy metal scavenger mechanism of humic acids. However, lead discharge increased both in the whole population and in the group with high blood lead levels

The changes of the parameters of indirect heavy metal metabolism are not unambiguous in the exposed groups: although the activity of DALA-dehydrogenase increased markedly and urine ALA decreased considerably, in the cadmium exposed groups the activity of DALA-dehydrogenase decreased considerably, in spite of the significant decrease of cadmium inhibiting enzymes which contain SH groups. However, in spite of the decreased activity, ALA urine discharge decreased. Calcium phosphate metabolism remained practically unchanged in groups with high cadmium levels.

During the two week HUMET[®]-R treatment the blood level of micro elements changed: zinc concentration remained practically unchanged over the whole population, but decreased insignificantly, by 15 to 18%, in groups with high blood levels of heavy metals (lead and cadmium).

The level of serum copper increased significantly by 17.6%. The treatment also had a favorable effect on the blue plasmin level: the concentration of carrier protein increased.

This short run treatment had no considerable effect on erythrocyte production. The parameters of iron metabolism change are ambiguous: the highly visible increase in serum iron levels (3 to 23.7%) is counter-balanced by significant serum ferritin decrease (-13.5 to +3.9%) and a slight increase of the full iron bonding capability (1.7% to 4.7%).

Answers to the questions raised under *The Study's Objectives*:

1. HUMET[®]-R did not influence hematopoiesis during the two week treatment. Iron metabolism increased as a result of the treatment.
2. The studied product had practically no effect on general laboratory parameters.
3. HUMET[®]-R significantly decreases the blood's lead and cadmium levels and promotes the discharge of harmful heavy metals
4. The product significantly raised the level of the trace element copper.
5. The heavy metal decreasing effect of HUMET[®]-R is more marked in the case of higher initial heavy metals

Based on the above results the studied product is promising with respect to the elimination of heavy metals, its primary effect, i.e. the decrease of heavy metal levels in the blood, can be noted after a relatively short, two week period of administration. However, the complex alterations of metabolism (micro element management and SH enzyme activity) caused by exposure to heavy metals can most certainly be corrected only by long term administration.

The present study reveals that HUMET[®]-R is a promising subject for clinical studies, where its effects on trace element and heavy metal metabolism must be analyzed in detail on selected patients (parenchymal liver damage, occupational and environmental exposure to heavy metals, etc.).

7. Tables

7.1. *The Demographic Figures of the Studied Population*

7.2. *Descriptive Statistical Results According to Sex*

7.3. *Hypothesis Testing - Whole Population*

7.4. *Hypothesis Testing - Cadmium Exposure*

7.5. *Hypothesis Testing - Lead Exposure*

8. Figures

8.1. *Changes of the Blood's Cadmium Level in Volunteers (14) with High Cadmium Levels ($\geq 0.08 \mu\text{mol/l}$)*

8.2. *Changes of the Blood's Lead Level in Volunteers (11) with High Lead Levels ($\geq 1.00 \mu\text{mol/l}$)*

7. Tables

7.1. Demographic data of the population

Parameter	Male	Female
Number of patients	25	26
Age (average)	38,20	40,00
SD	11,81	8,94
Minimum	18	21
Maximum	60	59

7.2. Descriptive statistics by sex groups

	Male			Female		
	Mean	SD	n	Mean	SD	n
HGB-B	9,837	1,049	21	8,767	0,645	25
HGB-A	9,568	0,560	21	8,876	0,448	25
HTK-B	0,457	0,026	21	0,408	0,040	25
HTK-A	0,460	0,022	21	0,419	0,030	25
FVS-B	6,486	1,080	21	6,018	0,747	25
FVS-A	6,341	1,276	21	6,266	0,724	25
FERR-B	186,367	136,102	23	52,609	36,268	23
FERR-A	143,883	79,907	23	62,883	41,793	23
FE-B	18,893	4,752	15	18,906	5,696	18
FE-A	21,053	5,897	15	20,233	6,576	18
TVK-B	64,000	7,473	13	64,600	11,230	16
TVK-A	67,038	7,362	13	67,606	13,489	16
GOT-B	25,037	10,915	19	22,900	8,237	22
GOT-A	23,084	7,894	19	23,014	8,814	22
GGT-B	24,512	13,765	18	25,745	10,867	22
GGT-A	24,794	9,563	18	30,745	22,135	22
AP-B	203,895	44,411	19	213,732	39,994	22
AP-A	218,905	44,145	19	216,223	80,641	22
CPLASM-B	32,013	9,464	9	41,938	10,818	6
CPLASM-A	38,964	15,538	9	41,397	17,441	6
ALAD-B	797,271	194,050	22	921,955	309,449	22
ALAD-A	806,982	261,652	22	890,818	204,586	22
NA-B	143,286	3,094	7	143,429	2,652	14
NA-A	142,857	2,795	7	143,429	2,681	14
K-B	1,000	0,311	7	3,979	0,176	14
K-A	1,041	0,445	7	4,063	0,325	14

	Male			Female		
	Mean	SD	n	Mean	SD	n
CA-B	2,433	0,111	15	2,506	0,106	18
CA-A	2,480	0,077	15	2,428	0,093	18
P-B	1,029	0,209	14	1,083	0,129	18
P-A	1,043	0,221	14	1,055	0,136	18
PB-B	0,892	0,743	25	0,630	0,415	26
PB-A	0,568	0,418	25	0,783	0,458	26
CD-B	0,084	0,158	19	0,167	0,270	18
CD-A	0,036	0,044	19	0,031	0,025	18
CU-B	12,202	2,732	21	12,452	4,334	23
CU-A	12,677	3,819	21	16,172	4,594	23
ZN-B	11,986	3,388	21	12,150	2,578	23
ZN-A	12,310	5,119	21	12,022	3,765	23
ALAU-B	42,805	16,091	20	38,754	18,322	24
ALAU-A	35,470	14,771	20	34,792	17,643	24
PBU-B	0,217	0,201	21	0,193	0,110	25
PBU-A	0,209	0,216	21	0,266	0,206	25
CDU-B	0,055	0,061	17	0,053	0,038	17
CDU-A	0,040	0,045	17	0,052	0,065	17

7.3. Hypotesis tests of population

Parameter	Mean	SD	n	t	p	Change in %
IIGB_B	9,256	1,001				
HGB_A	9,192	0,606	46	0,520	0,606	-0,7
IITK_B	0,430	0,042				
HTK_A	0,438	0,034	46	-1,318	0,194	1,6
FVS_B	6,232	0,933				
FVS_A	6,300	1,003	46	-0,408	0,685	1,1
FERR_B	119,488	119,463				
FERR_A	103,383	75,181	46	1,586	0,120	-13,5
FE_B	18,900	5,208				
FE_A	20,606	6,194	33	-1,520	0,138	9,0
TVK_B	64,331	9,570				
GOT_B	23,890	9,508				
GOT_A	23,046	8,296	41	0,492	0,625	-3,5
GGT_B	25,190	12,106				
GGT_A	28,068	17,683	40	-0,989	0,329	11,4
AP_B	209,173	41,856				
AP_A	217,466	65,520	41	-0,766	0,448	4,0
CPLASM_B	35,983	10,877				
CPLASM_A	39,937	15,752	15	-0,735	0,474	11,0
ALAD_B	859,614	262,931				
ALAD_A	848,900	235,953	44	0,220	0,827	-1,2

Parameter	Mean	SD	n	t	p	Change in %
NA_B	143,381	2,729				
NA_A	143,238	2,663	21	0,203	0,841	-0,1
K_B	3,986	0,420				
K_A	4,057	0,357	21	-0,684	0,502	1,8
CA_B	2,473	0,113				
CA_A	2,452	0,089	33	0,915	0,367	-0,8
P_B	1,059	0,168				
P_A	1,050	0,175	32	0,429	0,671	-0,9
PB_B	0,758	0,607				
PB_A	0,678	0,448	51	0,912	0,366	-10,7
CD_B	0,124	0,220				
CU_B	12,333	3,619				
ZN_B	12,071	2,957				
ZN_A	12,160	4,411	44	-0,106	0,916	0,7
ALAU_B	40,595	17,267				
ALAU_A	35,100	16,218	44	1,734	0,090	-13,5
PBU_B	0,204	0,157				
PBU_A	0,240	0,210	46	-0,821	0,416	17,6
CDU_B	0,054	0,050				
CDU_A	0,046	0,056	34	0,689	0,496	-14,1

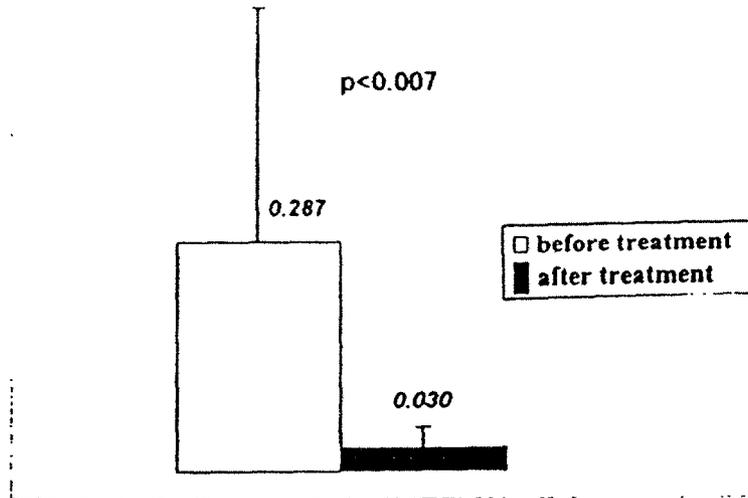
7.4. Hypotesis test by cadmium exposition

Parameter	Mean	SD	n	t	p	Change in %
HGB_B	8,834	0,709				
HGB_A	8,985	0,512	14	-1,599	0,134	1,7
IITK_B	0,419	0,042				
HTK_A	0,431	0,033	14	-1,191	0,255	2,6
FERR_B	109,633	135,401				
FERR_A	113,856	88,141	13	-0,202	0,844	3,9
FE_B	16,740	4,894				
FE_A	20,710	7,440	10	-1,378	0,202	23,7
TVK_B	63,289	12,781				
TVK_A	65,167	11,517	9	-1,016	0,339	3,0
CPLASM_B	35,918	14,049				
CPLASM_A	39,108	14,351	4	-0,254	0,816	8,9
ALAD_B	989,143	277,594				
ALAD_A	851,000	187,332	14	2,021	0,064	14,0

Parameter	Mean	SD	n	t	p	Change in %
CD_B	0,287	0,297				
CD_A	0,030	0,025	14	3,203	0,007	-89,5
CA_B	2,430	0,106				
CA_A	2,451	0,078	10	-0,598	0,564	0,9
P_B	1,050	0,227				
P_A	1,079	0,228	10	-0,586	0,572	2,8
CU_B	14,005	4,032				
CU_A	13,508	2,540	14	0,703	0,495	-3,5
ZN_B	13,589	3,205				
ZN_A	11,167	3,483	14	1,536	0,149	-17,8
ALAU_B	41,885	16,627				
ALAU_A	33,115	13,881	13	1,965	0,073	-20,9
CDU_B	0,093	0,053				
CDU_A	0,051	0,081	13	1,662	0,122	-43,0

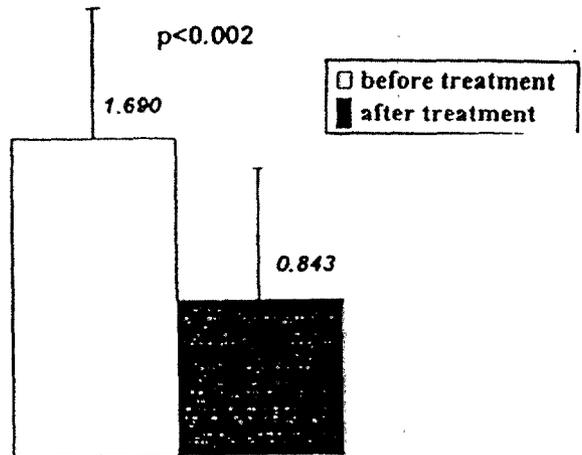
8. Figures

Change of blood cadmium level in patients group with high cadmium level ($\geq 0,08 \mu\text{mol}/\ell$)



1.figure

Change of blood lead level in patients group with high lead level ($\geq 1,0 \mu\text{mol}/\ell$)



2.figure

**IV. 1 STUDIES IN CLINICAL PHYSIOLOGY
AND PSYCHOLOGY**

IV. 1.1 Effects on the performance of elite athletes

Máté Petrekánits, M.Sc., Exercise Physiol. and Ergometry Lab., Chair of Health Science and Sports Medicine, Hungarian School of Physical Education, Budapest

Prevention implies primarily the preservation of health, respectively an improvement of physical fitness and mental performance. Thus the first question to ask is what effects HUMETA-R would bring about in a healthy human. The Chair of Health Science and Sports Medicine have been dealing with top sportsmen for many decades, and have been responsible for their regular monitoring since 13 years. Even elite athletes are incapable of maximum performance unless they are in an optimum condition physiologically. Their physical and physiological work capacity, performance, endurance and oxygen transport mechanisms need therefore consistent and regular checking. Top-level performance can only be expected of our athletes if the results of the laboratory studies lie within the normal physiological range. Of the multitude of data commonly used for the check-ups after an all-out exercise bout, long years of experience have shown that post-exercise peak blood lactate corrected for resting hematocrit, peak exercise heart rate and relative aerobic power per kg body mass, respectively their correlations are valid predictors of an athlete's condition.

The effect of taking HUMETA-R for 3 weeks was studied in groups of complaint-free first-class athletes, the criteria of their group assignment being the change occurring in resting hematocrit (Table 1.1). Athletes whose hematocrit became higher after the treatment were assigned to Group I, and the ones in whom it decreased under the treatment, to Group II.

Table 1.1: The effect of a 3-week HUMETA-R treatment on resting hematocrit and hemoglobin in top athletes (means and sd's).

Group	Hematocrit (Htc)			Hemoglobin (Hgb)		
	Before	After	Difference	Before	After	Difference
Group I (N = 12)	0.408 ±0.044	0.460 ±0.031	0.052** ±0.014	14.8 ±1.9	15.8 ±1.2	1.0* ±0.4
Group II (N = 13)	0.469 ±0.027	0.441 ±0.022	-0.028** ±0.004	16.3 ±0.9	15.5 ±0.7	-0.8** ±0.2
Both (N = 25)	0.440 ±0.047	0.450 ±0.028	0.010 ±0.092	15.6 ±1.6	15.7 ±1.0	0.1 ±0.2

Group I: Subjects in whom Htc was increased by the treatment.
 Group II: Subjects in whom Htc was decreased by the treatment.
 Both: Groups I + II. N = number of subjects. ** = P < 0.01, * = P < 0.05.

Differences between initial (zero time) and post-treatment means were tested by Student's t for dependent samples, while those between the means of the groups formed according to the observed effect by two-sample t-tests at the 5% level of random error.

When the athletic groups were joined (Table 1.1, Both), the differences between the means before and after the 3-week treatment were not significant; the values were in the middle of the physiological range. When related to the initial level, however, the change in Htc and Hgb became apparent, and the means after the 3-week HUMETA-R treatment could be found in the middle of the physiological (reference) range.

Irrespective of whether Htc values increased or decreased during the treatment, the sports performance of these 'top-gear' athletes showed no decrease but instead a number of their results (not detailed here) even improved.

Table 1.2: Post-exercise variables of athletes grouped by resting hematocrit (means and sd's).

Group Variable	Grand means (N = 59)	Htc < 0.43 (N = 18)	0.43 < Htc < 0.47 (N = 20)	Htc > 0.47 (N = 21)
Resting hematocrit (Htc: L/L)	0.45 ± 0.04	0.41 ± 0.02	0.45 ± 0.01	0.49 ± 0.02
Peak post-ex blood lactate (LA: mmol/L)	14.2 ± 2.7	14.8* ± 2.3	14.1 ± 3.3	13.1 ± 2.2
Peak exercise heart rate (HR: bpm)	185 ± 6.8	187 ± 4.5	186 ± 9.2	182 ± 5.9
RVO ₂ (O ₂ ml/min/kg b.w.)	63.8 ± 6.7	64.6 ± 4.8	61.7 ± 6.4	60.3 ± 3.8

Abbr.: RVO₂ = relative aerobic power.

* = P < 0.05 (ANOVA, F-test).

Table 1.3: Correlation coefficients between the exercise physiological variables of athletes grouped by their resting hematocrit.

Group	Htc vs LA	Htc vs HR	Htc vs RVO ₂	LA vs HR	LA vs RVO ₂	HR vs RVO ₂
Htc < 0.43	-0.04	0.05	0.11	0.14	-0.20	-0.08
0.43 < Htc < 0.47	0.17	0.25	0.19	0.02	-0.14	0.09
Htc > 0.47	0.10	0.16	-0.44*	0.22	-0.43*	0.33
All joined	0.25	0.18	0.29*	0.25	0.36**	0.39**

Symbols: * = P < 0.05 ** = P < 0.01.

In the next phase, therefore, untreated volunteer athletes were studied to see how the relationships (Table 1.3: Correlation analysis) of the observed physiological data would change compared to their starting values (Table 1.2).

The means for the athletes assigned to groups by their initial resting hematocrit were compared to one another and to the grand mean (Table 1.2). The mean lactate level of the athletes with a hematocrit level lower than 0.43 was different from that of the other two groups (P < 0.05).

Testing all the athletes, positive correlation was seen between Htc and $\dot{V}O_2$, further between LA and $\dot{V}O_2$, i.e. both Htc and lactate were proportionate to aerobic performance. On the other hand, the same relationships in the 'Htc > 0.47' group were negative. The mechanism of the phenomenon is yet unknown, but some authors (Salonen et al. 1992, Sullivan 1992) suggest that high serum ferritin level is a risk factor for myocardial infarction. If this assumption holds, the favorable effect of the 3-week HUMET®-R treatment is precisely an 'optimization' of hematocrit and hemoglobin values, i.e. it adjusts them to the physiological 'reference value'.

As a summary, it can be stated that HUMET®-R has physiological optimizing, balancing and performance improving effects as well.

IV. 1.2 Effects on the psychic activity of elite athletes

Agota Lénárt, M.Sc., Chair of Psychology, Hungarian School of Physical Education, Budapest

Athletes taking HUMETS-R syrup (HORIZON-MULTIPLAN Ltd., Budapest) have consistently reported on favorable psychic changes, such as recovering faster from training fatigue, needing less time for sleep, concentrating attention easier and more efficiently and on a feeling of improved general well-being within 3 to 5 days from starting the syrup.

A study using several of the nationally standardized psychological tests was therefore begun to check these impressions in subjects who volunteered to take the syrup daily for one month. The 11 subjects studied were all Class I male paddlers. Pre- and post-treatment physiological status was tested by an all-out treadmill exercise. The psychological tests employed were as follows:

- the AAI-H Hungarian inventory of anxiety and arousal intensity, constructed by El-Zahhar and Sipos;
- the F X-1 and X-2 values of the STAI-H inventory for state and trait anxiety of Spielberger standardized by Sipos for Hungary;
- Pieron's test to check the properties of attention (computer aided version with signal detection);
- Allmer's SLM test to check sport performance motivation;
- the Hungarian standardized version of Eysenck's inventory on personality factors (HEPQ);
- the PSIS test to assess the psychic readiness for competition;
- Lüscher's color test to study the non-conscious but active motives of the affective space;
- the revised and abbreviated version of Goldberg's general health inventory.

Basic statistics (means, sd's, coefficients of variation) and one-sample t-tests were computed from the data.

The post-treatment score of AAI-H for arousability increased by 2.5 (Fig. 2.1, $P < 0.05$). Indicating improved sociability and an optimistic, active attitude, the score of HEPQ for extroversion increased by 1.36. On the neuroticism scale a slight decrease of 1 point was seen.

The sport performance motivation test (SLM) showed a shift of +0.82 point in the capability of sustaining efforts during the trainings. However, this improvement may also be attributed to a better physical condition. Victory motivation also rose slightly. The sensitivity to the start excitement stress (Fig. 2.2, SLM Factor 6) decreased. The means of competitive athletes in general are in the range of 4.5 - 5.5 depending on the event of sport, with an sd of 2-3 points. In the present study the initial score of 6.36 decreased to 5.0 ($P < 0.05$), indicating a change towards a better adaptation.

Post-treatment PSIS scores displayed higher self-confidence and improved attitude to racing, though the differences did not reach the level of significance. In the Lüscher test, a shift toward a better balance of the vegetative index was observed (Fig. 2.3, the pre-exercise scores before and after the treatment were 1.19, resp. 0.89; the post-exercise ones being 1.11, resp. 0.97). The column index (VI O) also showed some change toward the score of 1.28 regarded as optimum and varied consistently within the healthy range (0.53 - 3.16) of the affective space.

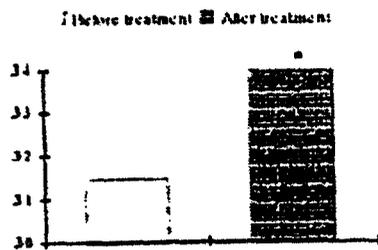


Fig. 2.1: Change in the grossability factor of the AAI-II test. Ordinate scaled in points. * = $P < 0.05$.

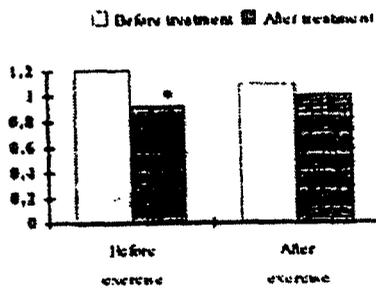


Fig. 2.2: Changes in the sensitivity to start excitement stress (SLM Factor 6). Ordinate scaled in points. * = $P < 0.05$

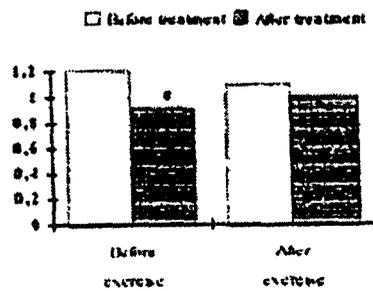


Fig. 2.3: Changes in the Vegetative Index 8.Fb of the Lüscher color test. Ordinate scaled in points. * = $P < 0.05$

is between 3-4 points, a symptom-free subjective state scoring as 0. The initial mean was 7.09 points. This then scaled at 4.27 after treatment, i.e. it approached the problem-free zone ($P < 0.05$)

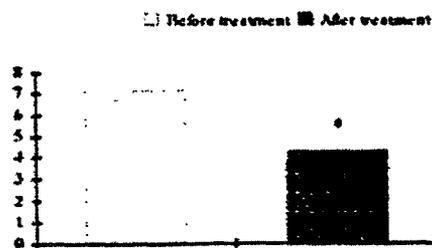


Fig. 2.6: Scores of the Goldberg General Health Inventory indicating an improved subjective well-being after treatment. Ordinate scaled in points. * = $P < 0.05$.

After the completion of the study, some subjects under treatment reported that their adjustment to inter-zone time lag in a foreign country, even when flying to a strong race, was easier and faster. Several of the subjects have found the syrup 'mobilized energy resources' without exhausting them so they could maintain their 'sport form' easier, a great help in form timing. Later continuation of taking the syrup depended on whether they felt a need of it. They reported also about the impression that once they had reached 'top shape' they felt no or less need of it.

None of the test subjects had to discontinue the treatment because of side effects, though two of them reported transitory digestion problems and nausea when taking the syrup. For athletes, some other drug form may be more preferable in the future.

In summary, favorable changes were found with the preparation, both in subjective well-being and in the restoration of mild emotional disorders. Stress resistance and concentration improved and were associated with an elevated arousal level. The syrup exerted an optimizing, balancing effect on the athletes. Significant improvements were seen in the Goldberg, Lüscher, SLM and Picron tests. The subjects reported on a decreased need for sleep, yet they awoke more refreshed. Parallel to an objective increase in focusing attention, the subjects experienced a subjective improvement of mental capacity. They tolerated even extreme training stress better.

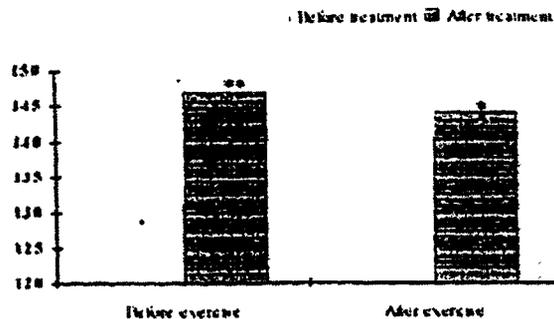


Fig. 2.4: Changes in the number of correct omissions of response (left pair) and of correct responses (right pair) in the Pieron test of attention. Ordinate scaled in points. Abbr.: exercise = an all-out exercise bout. ** = $P < 0.01$, * = $P < 0.05$.

The number of correct omissions of response improved by 15 points (Fig. 2.4, $P < 0.01$) after the treatment while the number of correct responses improved by 4 ($P < 0.05$). False alarms (when the person responds to a stimulus not to be answered) decreased by 15 points ($P < 0.01$). The difference of the pre- and post-treatment means for overall performance in concentrating attention (index T; Fig. 2.5) before an all-out exercise bout was 56 points ($P < 0.01$). The change in the post-exercise score was 16 ($P < 0.05$).

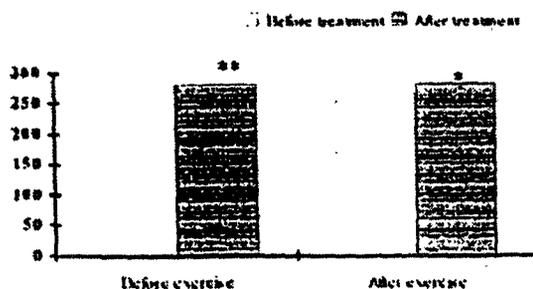


Fig. 2.5: Changes of the cumulative T-index of performance in the Pieron test of attention. Ordinate scaled in points. ** = $P < 0.01$, * = $P < 0.05$.

The favorable changes as assessed by the Goldberg General Health Inventory concerning subjective well-being after the treatment were quite remarkable (Fig. 2.6). In the abbreviated version, momentary symptoms are in the foreground rather than personality traits. According to the employed GHQ scoring (its advantage is that it reduces both the errors due to possible bimodal responses, and the problem of weighing between the columns), the upper limit between problem-free subjects and 'cases'

IV. 2 CLINICAL STUDIES

IV. 2.1 Serum iron

Miklós Molnár, M.D. and György Szabó, M.D.
Institute of Public Health of the Hungarian Railways, Budapest

Studies 2.1 and 2.2 were performed in the Occupational Health Laboratory of the Institute. The volunteers were selected from among 104 men and women (age: 18-65 years) reporting for health screening. They declared themselves healthy and after an informed consent they agreed to take the syrup as instructed for three weeks and abstain from other drugs during the study.

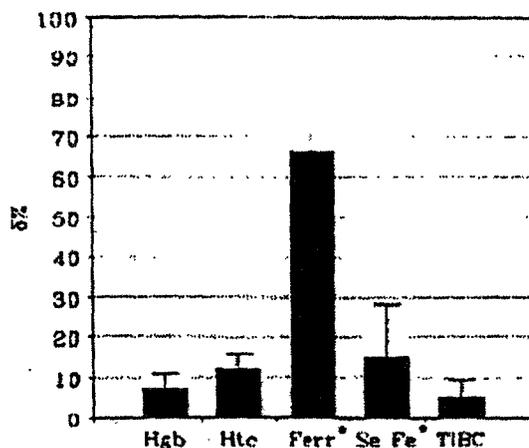


Fig. 2.1: Percentage changes in the studied hematological and clinical laboratory variables in subjects with a serum ferritin level below 20.0 µg/L (N = 14). Abbr.: Hgb = hemoglobin, Htc = hematocrit, Ferr* = serum ferritin, Se Fe* = serum iron, TIBC = total iron binding capacity. * = P < 0.05.

Of the volunteers 14 had a serum ferritin level of less than 20.0 µg/L. Percentage changes in the clinical laboratory data of these subjects are shown in Fig. 2.1, and Table 2.1 contains the details. All this occurred in a relatively short time, i.e. within 3 weeks.

Under the effect of the syrup treatment, ferritin levels approached a common physiological range, such that low values became higher while high ones decreased. The observation of low values becoming higher is easily interpretable: it indicates an improvement of iron deficient anemia. There is less knowledge about the interpretation of high ferritin levels, some authors (Salonen et al. 1992, Sullivan 1992) claim it is a risk factor of cardiac infarction.

Table 2.1: Changes in the iron metabolism of the subjects with a ferritin level below 20 µg/L.

Variable and unit	Before treatment		After treatment	
	Mean	SEM	Mean	SEM
Hemoglobin (mmol/L)	7.80	0.45	8.37	0.29
Hematocrit (L/L)	0.36	0.02	0.41	0.01
Serum ferritin (µg/L)	12.23	1.37	20.35	4.33
Serum iron (µmol/L)	12.58	1.48	14.46	2.58
Total iron binding capacity (µmol/L)	76.49	2.16	80.51	3.14

The observations indicated that the HUMET-R syrup, by providing for the recommended daily allowance of essential micro-elements independently from nutritional intake, is suitable for replenishing the iron stores.

IV. 2.2 Blood lead and blood cadmium levels

Miklós Molnár, M.D., Institute of Public Health of the Hungarian Railways, Budapest

The aim of the experiment was to study whether a 3-week HUMET-R treatment of workers coming for routine check-ups of occupational health would modify blood lead or blood cadmium levels near or above the health risk limit.

Blood chemistry of the subjects (mean, SEM and subject number) showed no pathological changes (GOT = 29.2 ± 1.71 U/L, N = 85; GGT = 37.35 ± 3.23 U/L, N = 84; cholesterol = 4.91 ± 0.16 mmol/L, N = 48; triglycerides = 1.00 ± 0.07 mmol/L, N = 48). At the first measurement, 21 subjects had blood lead concentrations higher than 1 µmol/L (health risk limit = 1.5 µmol/L), and in 26 subjects the blood cadmium level exceeded the health risk limit of 0.08 µmol/L.

Hemoglobin was measured by a Linson Junior model photometer, hematocrit by parallel glass capillary samples, centrifuged at 10,000×g (Mechanika Precyzyjna Microhaematocrit Centrifuge Type 316, Poland) for 5 minutes, ferritin was estimated by the ELISA technique (EAR-400), delta-aminolevulinic acid as suggested by the brochure on methodology published by the National Institute of Occupational Hygiene, Budapest (OMŰI), blood lead (Blood Pb) and cadmium (Blood Cd) levels by a Pye-Unicam SP-1900 model atomic absorption photometer. The differences were tested for significance by the one-sample t-test.

Hemoglobin, ferritin and DALA values were unaffected by the syrup treatment. The hematocrit values showed a biologically negligible change, whereas blood lead and cadmium levels had decreased remarkably (Tables 2.2 and 2.3).

Table 2.2: Changes observed in the subjects exposed to lead contamination (blood lead > 1 µmol/L; means ± SEM).

Parameter	N	Before treatment	Post-treatment difference	P
HGB (mmol/L)	18	9.42±0.18	-0.16±0.09	
HTC (L/L)	18	0.45±0.01	-0.01±0.01	<0.05
FERR (µg/L)	14	246.9±99.3	-21.1±21.1	
DALA (µmol/L)	12	761±74.3	114±73.0	
Blood Pb (µmol/L)	21	1.74±0.19	-0.73±0.19	<0.01

Abbr.: HGB = hemoglobin, HTC = hematocrit, FERR = ferritin, DALA = delta-aminolevulinic acid. Blood Pb = blood lead level, P = level of random error in the t-test for dependent samples. N = subject number.

Table 2.3: Changes observed in the subjects exposed to cadmium contamination (blood cadmium > 0.06 µmol/L; means ± SEM).

Parameter	N	Before treatment	Post-treatment difference	P
HGB (mmol/L)	25	8.91±0.25	0.11±0.13	
HTC (L/L)	25	0.41±0.01	0.017±0.007	<0.05
FERR (µg/L)	23	194.4±71.2	25.1±39.3	
DALA (µmol/L)	23	917±57.3	-44.8±55.2	
Blood Cd (µmol/L)	26	0.23±0.05	-0.19±0.05	<0.01

Abbr.: As in Table 2.1 and Blood Cd = blood cadmium level.

The observations indicated that the *HUMET®-R* syrup, besides supplying the recommended daily allowance of essential micro-elements independently from nutrition, was a suitable means also for decreasing the blood concentration of the heavy metals (lead and cadmium) representing the highest risk of environmental pollution. Further studies are necessary to clarify the details of the mechanism.

IV. 2.3 Lead poisoning caused by adulterated paprika

Iván Székely, M.D., Ward IV of Internal Medicine, Szt. György Hospital, Székesfehérvár

Absorbed lead becomes bound to the cells, first to erythrocytes, then to the cells of the liver and kidney. Later it is deposited in the bones as Pb-hydroxy-apatite. Its elimination is extremely slow with a biological half-time of 32 years. Studies recently published in the United States have demonstrated that small children develop mental disorders under exposure to lead even in quantities regarded up to now as non-hazardous, such that their IQ would decrease. This is why WHO halved the risk level in 1994.

The symptoms of lead intoxication are non-specific. It is easy to understand why in cases of a loss of appetite, fatigability, vague lower abdominal complaints the physician is unlikely to think first of lead poisoning, in particular since in our days manifest lead intoxication is very rare due to strict occupational health regulations in the industry and trade. In the past 15 years there were merely two cases (unskilled workers dismantling batteries) in Fejér county. Alimentary lead intoxication is even rarer. In the past 20 years there were only two small children in the whole country who were reported to have suffered lead intoxication from tea drunk from a lead enamelled terracotta vessel.

Between August and October 1994 altogether 9 patients were treated in our Ward for lead poisoning caused by adulterated paprika the color of which the smugglers enhanced by adding red lead. Lead levels, initially between 3 and 6 $\mu\text{mol/L}$ in the more severe cases, decreased quickly and spectacularly under infusion treatment with Ca-Na-EDTA followed by Byanodine_® (penicillamine) administration, with parallel clinical improvement. Every patient became symptom-free by the third day of treatment.

Six other patients, in whom either intoxication was milder and EDTA therapy was unnecessary, or showed Byanodine_® side-effects (two cases), took the natural chelating agent HUMET_®-R (supplied by HORIZON-MULTIPLAN Ltd. Budapest) for 3 weeks, and this treatment too helped to restore normal blood lead level at practically the same rate as did penicillamine. Except one case, lead levels had markedly decreased proving the efficiency of the preparation. Milder side effects were reported by two patients; nevertheless, their syrup therapy was stopped.

When patients report not really typical symptoms or syndromes, physicians ought to consider lead poisoning as one of the possible causes since as soon as the proper diagnosis is found recovery is fast and spectacular.

IV. 2.4 High occupational lead exposure

Csaba Flórián, M.D. Primary Medical Care System Outpatient Clinic, Ajka Crystal Ltd., Ajka

In the Ajka Glass Factory hollow and crystal glassware are produced with a semi-manual technology. Chronic lead contamination of the workers had been a special problem for years. Both the occupational health service and the management had made serious efforts to solve the problem.

The aim of the study was to detect whether the revitalizing syrup HUMET[®]-R, through its metal exchanger effect, would accelerate the elimination of the heavy metal accumulated in the subjects exposed to high lead intoxication risk.

The study run by the Primary Medical Care System of Ajka was performed in the factory consulting room of the Crystal Ltd. The study protocol was approved by the Chair of the Ethical Committee of the Hungarian Chamber of Physicians of Veszprém county. Exclusion criteria were: suspicion of lead intoxication, pregnancy, breast-feeding, renal, hepatic or heart insufficiency, circulatory and/or respiratory disorder, neurological or psychiatric disorder, allergy, diabetes mellitus, any permanent need of drug treatment (except oral contraceptives), alcohol and/or drug abuse. No exclusions occurred.

After obtaining written informed consent, 35 volunteers were selected (as specified in the protocol) in whom the usual quarterly zinc-protoporphyrine (ZPP) screening found a blood lead level between 1.00 and 2.99 $\mu\text{mol/L}$. By using random assignment, 20 subjects were selected as test subjects and 15 for control (altogether 14 men and 21 women, aged between 18 and 50 years). The observation period was 6 weeks. Tests were performed on Days 0, 21 and 42 \pm 3.

HUMET[®]-R syrup was supplied by HORIZON-MULTIPLAN Ltd., Budapest. The subjects took the syrup in the conventional dose of 20 ml diluted in 100-200 ml peach juice once daily after lunch.

Data recorded in the individual data sheets were: health status, body weight, blood pressure, MCV, MCH, MCHC, RBC, HTC, HGB, serum iron, transferrin, ferritin, creatinine, GOT, GPT, ZPP, blood lead and urinalysis (density, pH, protein, sugar, acetone, urobilinogen, sediment).

ZPP was determined by an AVIV model hemato-fluorometer, blood lead by atomic absorption spectrophotometry. Ferritin tests were performed by the Enzyme Diagnostics Laboratory of the Institute of Public Health of the Hungarian Railways, Budapest, while the other tests were carried out in the local clinical laboratory using standard methods.

Mean differences between initial and end results within a group were tested by one-sample t-tests, those between the two groups by two-sample t-tests.

At the first measurement, none of the control group showed lead levels above the health risk limit. Altogether 18 subjects of it were smokers with 10 to 30 cigarettes daily. In the test group there were 12 smokers (6 men and 6 women).

Table 2.4: Clinical laboratory studies in subjects exposed to lead (mean and SD).

Measurement Group/Variable	Initial		Day 21±3		Day 42±3	
	HUMET	Control	HUMET	Control	HUMET	Control
MCV μ L	94.0±5.5	91.9±3.8	93.2±5.8	93.4±3.2	94.7±5.2	92.3±3.5
MCH pg	31.5±1.9	30.7±1.5	31.4±1.9	30.9±1.0	30.9±1.9	30.1±1.0
MCHC g/L	335±7.3	334±8.2	330±7.4	331±7.2	327±7.0	327±8.3
RBC T/L	4.47±0.38	4.73±0.39	4.51±0.35	4.66±0.34	4.51±0.35	4.76±0.35
HTC L/L	0.42±0.03	0.43±0.04	0.43±0.04	0.44±0.03	0.43±0.03	0.44±0.03
HGB g/L	140±9.4	144±11.8	142±10.6	144±9.6	139±8.0	143±9.7
Se-creatinine μ mol/L	94.3±12.2	99.6±17.0	94.8±11.4	99.4±15.2	92.1±10.6	99.1±15.2
GOT U/L	37±33	30±13	26±17	23±8	33±24	27±10
GPT U/L	27±14	27±19	21±11	23±11	33±23	31±31
Se-iron μ mol/L	16.8±4.8	17.3±6.7	17.5±6.0	17.2±2.6	16.6±6.0	17.7±4.9
Transferrin μ mol/L	63.0±8.4	67.1±9.4	65.2±9.0	67.4±6.9	67.2±8.4	68.5±6.1
Ferritin μ g/L	42.5±41.8	66.1±70.3	41.2±43.4	53.0±44.1	43.4±36.8	68.2±61.9
ZPP μ mol/mol hem	185±81	169±87	220±102	202±109	235±111	196±105
Blood Pb μ mol/L	1.86±0.31	1.46±0.47	1.65±0.55	1.61±0.68	1.46±0.61	1.36±0.48

Table 2.5: Differences between post-treatment, interim and initial values in subjects exposed to lead (mean, SEM and significance).

Differences	Group HUMETA-R		Control group	
Blood-Pb 2-1 μ mol/L	-0.21±0.12	n.s.	0.11±0.15	n.s.
Blood-Pb 3-2 μ mol/L	-0.19±0.07	<0.01	0.27±0.15	n.s.
Blood-Pb 3-1 μ mol/L	-0.40±0.11	<0.001	0.16±0.09	n.s.
ZPP 2-1 μ mol/mol hem	34.3±7.7	<0.001	33.0±16.2	<0.05
ZPP 3-2 μ mol/mol hem	15.4±5.6	<0.01	-9.0±18.3	n.s.
ZPP 3-1 μ mol/mol hem	49.7±10.8	<0.001	24.0±9.4	n.s.
Serum iron 3-1 μ mol/L	0.9±1.8	n.s.	-0.11±1.8	n.s.
Serum iron 3-2 μ mol/L	-1.4±1.8	n.s.	0.2±1.1	n.s.
Serum iron 3-1 μ mol/L	-0.5±1.6	n.s.	0.1±2.0	n.s.
Ferritin 2-1 μ g/L	-1.3±2.6	n.s.	-11.1±7.6	n.s.
Ferritin 3-2 μ g/L	2.1±4.1	n.s.	10.6±6.3	n.s.
Ferritin 3-1 μ g/L	0.8±3.0	n.s.	-0.4±5.3	n.s.

Abbr.: Numbers after the variables denote measurement. Pb = lead, ZPP = zinc-protoporphyrine.

MCV, MCH, MCHC, RBC, HTC, HGB, serum creatinine, GOT, GPT and iron metabolism (Table 2.4) did not change. Neither systolic, nor diastolic blood pressure means showed changes during the treatment. As a result of the 6-week syrup treatment, blood lead levels decreased markedly and significantly (Table 2.5).

In the period observed, mild and transitory diarrhoea was seen in two subjects, which normalized without stopping the treatment. Four subjects reported moderate nausea and one a transitory headache.

The treatment was stopped because of febrility in 2 female subjects, and there was one male subject in the control group who refused collaboration for unknown reasons.

It has been concluded that the HUMETA-R syrup can be employed also as a preventive measure when subjects exposed occupationally to contamination are suspect of lead absorption.

IV. 2.5 Alopecia patients

László Kovács, M.D., and Ferenc Köhégyi, M.Sc., Hódmezővásárhely

Alopecia, a common dermatological pattern, is hair loss that develops as a result of an impaired hair bulb and hair follicle system

The aim of the study was to check the effect of HUMET[®]-R syrup, a humic acid - metal complex product (supplied by HORIZON-MULTIPLAN Ltd), on reversible alopecias. Alterations of this kind may develop either diffusely, under the effect of chemotherapy, inflammations, infections, chemical or drug effects, in chronic and hormonal diseases, or else in sharply defined areas, due to psychic stress, mechanical causes, inflammatory diseases or foci, thyroid disorders, but also in iron and zinc deficiency.

Treatments (the syrup or placebo contrast) arranged as a double-blind experiment were employed for 4 to 6 weeks in 54 patients (28 women and 26 men, aged between 33-36 years) of diffuse (N = 42) and areal (N = 9) alopecia, and in further three patients for reasons other than hair loss. Of the alopecia cases 29 could be evaluated from the group treated with the HUMET[®]-R preparation and 11 of the placebo group, because 10 patients did not report again. Blood zinc and iron were measured both at the beginning and end of the study. Before and after treatment, skin samples of 2 mm diameter were excised from the temporo-parietal region for a zinc content assay by atomic absorption photometry (study still in progress).

There were no practical differences in the type and duration of alopecias between the test and placebo groups. The history of the ailment ranged between one month and 20 years, with a mean duration of complaints of 3.5 - 4 years. Trichogram studies were performed in all patients at the outset and in the follow-up phase.

The treatment of alopecia with HUMET[®]-R gave excellent results in 12 cases, good in two, and moderate in nine cases. The symptoms remained unchanged in six cases. In the placebo group, excellent results were found in two cases, good in one and moderate in five cases. No change was seen in three patients. *The HUMET[®]-R group had a remarkably greater number of excellent and good results.* In this group the most conspicuous observation was a change in the proportion of dystrophic hair, while in the placebo group the anagen phase was dominant.

In the test group, the follow-up tests found blood zinc to be lower than before the treatment (24.7 vs. 16.7 $\mu\text{mol/L}$). The same was more marked in the placebo group (39.5 vs. 18.8 $\mu\text{mol/L}$). On the other hand, serum iron rose in both the HUMET[®]-R (15.7 vs. 19.1 $\mu\text{mol/L}$) and the placebo (21.8 vs. 23.5 $\mu\text{mol/L}$) groups in weeks 4 through 6 of the treatment. In the group treated by HUMET[®]-R, blood zinc showed a more marked decrease in the cases whose response was good than in those with a moderate or weak response. While zinc level also decreased in both of the placebo subgroups, this was more marked in those with a poor response.

In the HUMETS-R group higher serum iron values were seen in the 'good response' patients, while iron levels showed little or no change in the subjects giving a poorer response. In the placebo group there was no appreciable difference in serum iron between the two response types.

As the syrup had been used to maintain or restore physical and psychic performance of athletes since long, possible changes in the *mental and physical condition* of the alopecia patients were also studied. In the HUMETS-R group these attributes improved in 11 patients, remained unchanged in 17, and became worse in one. The respective results were two, seven and two in the placebo group.

The role of zinc and iron is so well known in the pathogenesis of alopecias that the prescription of an iron or zinc preparation is practically automatic. However, there is some evidence now that from the zinc salts that had been prescribed in dermatological practice nearly nothing is likely to become adsorbed. There is yet no accurate knowledge about the part the other trace elements in the syrup may play in alopecia therapy. It is an interesting challenge to find out whether the good response to HUMETS-R therapy was due to some zinc uptake of the hair bulbs when serum iron rose and blood zinc fell. Information about this possibility is expected from the skin samples to be studied by atomic absorption photometry.

IV. 2.6 Tumor patients, Part I

(A SECONDARY ANALYSIS OF CSUCSKA'S OBSERVATIONS)

András Gellej, M.D., Hepatology Ward, Hospital of the Hungarian Railways, Budapest

The research work of Dr. Csucska as well as the fact that he gave humic acid preparation also to humans as an adjuvant in certain diseases was learned by the author in December 1991. Following the inventor's death his family was kind to give permission to study the notes the inventor used to record the data of such patients. While analyzing these cases, the author also started the follow-up care of those that still wished to take the preparation. The present paper summarizes some of the experiences.

Between 1978 and 1993 altogether 229 persons with different diseases took the humic acid preparation as a trace element replenisher, 91 of whom were tumor patients. Of these, altogether 64 case histories could be processed. Along with the treatment prescribed by their physicians, these patients took the preparation daily for at least 3 months. Csucska recommended tumor patients to take it continuously for one year at most, then to have a 60-day cure in every quarter of a year, generally through one or two years, and to close this regimen by 60-day periods repeated every half year.

In evaluating these data, these patients were grouped by their health status into categories of recovered, improved, unchanged, deteriorated and unknown condition. Tracing of the fifth group continues, so results may still change as information grows.

The variables of data processing depended on the nature of the original documentation: personal data, diagnosis, tumor localization and histopathology, the final reports of the hospitals and any intercurrent surgical, radiation and chemo-therapeutic measures, adding where available past and present clinical status using WHO's "TNM-System" stages.

Surgery was recorded either as total extirpation (completely tumor-free status), palliative intervention, or one limited to histological sampling. When the preparation was used also during radiation or cytostatic therapy or else discontinued for the time of the treatment, this fact was also recorded. Additional data studied about the treatment with the humic acid preparation were: starting time, duration in months and mode of treatment, any change in the main therapy of the tumor and in the clinical status until the last date available. Status changes were numbered, rising from quick remission through gradual remission, unchanged condition and deterioration to death.

It is noted that along with the general and consistent oral way, the possible other application modes of the preparation were inhalation, irrigation, tampons or external for certain skin lesions. Table 2.6 shows the patients' status and Table 2.7 the organ loci. For this analysis, patients free of tumors for a longer time were regarded as 'recovered ones', respectively as 'improved' if either objective tumor size decreased or the patient reported subjective health improvement. They were termed 'unchanged' if tumor development stopped and they could adapt their life to the neoplastic disease. The cases in which neither medical therapy nor humo-chelate revitalizing could stop a decline of health, were qualified as 'deteriorated'. Data on weight changes and subjective symptoms are reproduced in Table 2.8.

Table 2.6: Distribution of status and availability of histology of the 64 tumor patients studied.

Condition Stage	Recovered		Improved		Unchanged		Deteriorated	
	#	Histology	#	Histology	#	Histology	#	Histology
I-II	6	6	7	5	3	2	1	1
III	6	6	6	2	0	0	2	1
IV	5	3	14	12	5	5	9	6
Total	17	15	27	19	8	7	12	8

Table 2.7: Organ localization of tumors.

Localization	Patients	Histology available
Intestines	28	16
Lungs	12	10
Stomach	7	0
Lymphoid tissue	6	0
Breast	6	2

Table 2.8: Subjective status of the tumor patients.

Feels well	38
Appetite improved	30
Weight gained	27
Pain decreased	12

Statistics of the adverse effects: six patients reported heartburn during administration of the humic acid preparation, one of them abandoned this kind of treatment because of it. One patient complained of 'a burning sensation in the esophagus'.

IV. 2.7 Tumor patients, Part II

Károly Györfy, M.D., Kaposi Mór Hospital, Kaposvár

Experience gained since September 1994 in altogether 81 tumor patients is reported. The syrup preparation HUMETA-R was used always as an adjuvant treatment supporting main therapy. The observations involved three aspects: the extent of subjective remission, any effect on hematopoiesis, and any decrease of edema.

The neoplastic growth affected the breast in 34 cases, the stomach or intestines in 8, the female reproductive organs in 8, the lungs in 7, the urogenital system in 3 cases. There were two cases of melanoma malignum. The rest of the patients had tumors of miscellaneous origin.

The objective of administering the syrup was to ease the grave condition of these patients and so far as possible to better somewhat the quality of their life. At least a part of this goal could be reached in the majority of the patients. Their general condition improved, they tolerated cytostatic therapy better. The effect on hematopoiesis was also obvious: the preparation increased erythrocyte counts so there was no need for other iron supplementation. Also white blood cell counts rose consistently. In several cases post-operative arm edema following breast surgery was less marked.

A discontinuation of the syrup administration was necessary in five patients because of stomach complaints and nausea. Except for these, HUMETA-R was found to help mitigate several of the complaints associated with malignancy and complemented traditional therapy well.

The importance of avoiding any additional harassment that adjuvant treatments may cause to a patient already severely distressed by the gastrointestinal and hematopoietic side effects of chemical or radiation therapy is emphatically stressed. In this respect, patients reported the HUMETA-R syrup as a very humane preparation. It should be noted that patients in the terminal stage appreciate any, even a subjective improvement of life quality.

IV. 2.8 Tumor patients, Part III

Györgyi Kiss, M.D., Ilona Fritcz, M.D., and Gábor Kónyves, M.D., Hódmezővásárhely

By now, altogether 21 patients (six men and 15 women, aged between 24 and 72, respectively 38 and 74 years) have taken HUMETA-R under the care of the authors. Five of the patients have died by now. They have been randomly selected, with their informed consent in each case. Tumor diagnoses (lymphomatic, mammal, pulmonary, rectal and urogenital neoplasms, most of them with metastases, and malignant dermatomyositis) were histologically verified by the hospitals responsible for their treatment. Family doctors like the authors are not involved in specific tumor therapy, continuous cytostatic or chemotherapy was the duty of the hospitals in which the diagnosis was made.

The patients took HUMET[®]-R syrup in the recommended single daily dose only in the periods that were not engaged by specific tumor therapy. Duration of this kind of adjuvant treatment ranges now between one and 18 months and has associated with positive changes including weight gain, near normal hematologic status even along with cytostatic or radiation treatment, a reduced need for analgesics and an improvement of physical and psychic stress tolerance, often a restoration of an active life, even the capability to work. In most of these patients depression so characteristic of tumor cases did not develop at all, an evidence of improved quality of life.

IV. 2.9 Tumor patients, Part IV

Miklós Molnár, M.D. Institute of Public Health of the Hungarian Railways, Budapest

During their protracted disease most of the tumor patients have to face a steady deterioration of physical condition. They lose weight, blood cell counts fall, they become anemic, have gastrointestinal disorders and usually suffer from growing pains.

The preparation was recommended as a revitalizing agent to the tumor patients. These patients have been followed only for two years until now so only some initial experience can be reported. Most of these early results are good or at least very promising.

Micro-element supplementation has restored hematopoiesis quickly and normalized functional enzyme disorders too. The patients' condition usually changed for the better as early as in the first week of taking the revitalizer. They felt stronger, their appetite returned, they needed less sleep and awoke in a better condition, more refreshed. Pains, if any, generally decreased or ceased, so less painkillers were necessary. The patients' attitude to life improved, their depression diminished, even bed-ridden patients often got up and lived a more active life of better quality.

Nevertheless, it must be stated beyond a doubt that HUMET[®]-R is by no means a panacea or a cure-for-all agent. In the same way as done with the excellent results, facts about personal tragedies, which often cannot be avoided, should also be reported. So, for instance, a 50-year old man recently operated for lung carcinoma started taking HUMET[®]-R as soon as his disease was detected. Yet, brain metastases appeared already two months after surgery, and the patient soon died.

Another but more reassuring example of this kind was a patient with breast cancer who took the preparation for half a year after surgery. Her decline was very quick, she died within 3-4 days, but until that time she felt excellently, gained several kilograms, was able to work and was very hopeful throughout. The observation that until a rapid premonitory decline patients maintain a tolerable condition has repeatedly been reported by the relatives of also other malignancy cases taking the syrup.

It must be stressed that the preparation is by no means a specific agent. It will 'only' increase general stress resistance and has a revitalizing effect. In these conditions, however, any improvement of the quality of life is a tremendous advantage for both the suffering patients and the physicians caring for them.

IV. 2.10 Pediatric diseases

Péter Szűts, M.D., and Péter Kószó, M.D., Children's Ward, Erzsébet Hospital,
Hódmezővásárhely

Ever since trace element deficiency was found to be the background of a number of diseases, efforts to introduce the missing elements into the organism have kept renewing. Practical experience has shown, however, that administering them as inorganic salts is far less efficient than expected. On the other hand, these metals and other essential elements were easily absorbed when bound to organic compounds, and in this way relatively small quantities sufficed to replenish the stores. The nature of such organic bonds must be, nevertheless, carefully considered. One merely has to refer to breast milk the iron content of which is lower than that of cow milk, yet the latter may induce anemia. The explanation is that essential metals, while basically hydrophilic, have to pass hydrophobic bio-membranes. These elements must therefore be transformed into hydrophobic complexes to cross them. In both therapy and replenishment it has already been realized by many of the experts that in supplementing trace elements the complex nature of the carrier molecule as well as of the element spectrum provided should be preferred to the replacement of individual metals and to inorganic forms.

The aim of the studies in progress in our ward has been to clarify what effects the HUMETA-R syrup might have in certain important childhood diseases, what side effects have to be reckoned with and what exactly the disorders are in which it should be recommended, both to the parents and to pediatricians, as an adjuvant worth knowing of in pediatric care.

In our ward, the syrup has been used for iron supplementation (as monotherapy) in hypochromic anemias, in all types of anorexia, in chronic eczema (either as monotherapy, both orally and locally, or in combination with earlier individual local therapies) as well as to accelerate recovery from any illness. The preparation was tested in certain forms of alopecia, too.

In all the cases a written approval was asked from the parents before starting the therapy. They were informed that if they did not want the HUMETA-R treatment, their children would receive the traditional standard therapy, and that refusing HUMETA-R treatment then or later would not involve any disadvantage to them.

Up to now, altogether 19 cases of *iron-deficient anemia* are available for evaluation. A marked rise of serum iron occurred consistently as early as two weeks after the start of the syrup therapy. The treatments lasted 3 weeks, the dose of 3 ml/10 kg b.w. was halved and administered twice daily diluted in water. Serum iron stayed normal when checked two weeks after completion of the cure.

HUMETA-R being a revitalizing agent, it was very important to ask the parents' opinion about the general status and appetite of the child. A surprising *improvement of appetite was reported in all children with iron deficiency*, a rather infrequent feature with the usual iron therapy.

The expected marked decrease of iron binding capacity did not occur in all cases, in some children it even rose. This has been assumed to arise from the fact that a part of the humic acids — compounds also normally present in the organism — became absorbed and behaved as additional carriers, so *transferrin levels decreased less than expected, in spite of an improving iron level and better general condition.*

Hemoglobin level rose in a part of the cases while in others it unexpectedly fell. When first observed, the decrease was rather confusing since the clinical response was equally good. Studies carried out by the University of Physical Education in athletes had given similar results previously, so the experience is not unique. All the 19 patients with anemia reported on a better appetite. *Improvement of mental and physical performance was marked in 13 cases, general condition became better in 14 of the 19 children.*

Another group of children giving surprising response were the cases of *chronic, therapy-resistant eczema* of which 8 patients have been studied. These children had already been seen by several, sometimes several dozens of clinics, had tried hundreds of ointments, arriving at a confirmation of the diagnosis at most, because improvement, if any, was transitory and not necessarily therapy-related

Such patients usually have eczematous phenomena all over their body and are harassed by continual and severe itching, especially in the typical areas. In 8 of the 9 cases treated by HUMETS-R a *marked improvement of the skin* took place. Syrup treatment had to be stopped in one case. The observation that the children were relieved from the otherwise unceasing, night-and-day itching already after a few days of application and could sleep undisturbed, was rather conspicuous. Both the parents and the physicians were sorry to see, however, that some days after the completion of the pre-scheduled 3-week treatment the ailment began to exacerbate again. It is very likely that this kind of skin pathology needs a more prolonged or even permanent treatment.

In summary, *HUMETS-R syrup, both as an adjuvant and as a medicament, appears to be of great help in improving the general condition of children suffering from certain diseases that cause much concern, and it does so with a negligible frequency of side effects.*

IV.3 SUMMARY

Results of commissioned clinical studies:

- a) HUMET®-R decreased blood lead and cadmium levels when these were above health risk limit.
- b) It optimized serum iron level by increasing it when hematocrit was low and decreasing it when hematocrit was high. This effect was manifest also in elite athletes who experienced that it benefited performance as well. In addition, the syrup exerted a favorable effect on their subjective well-being and mild emotional deviations, improved physical and mental stress tolerance as well as arousal level and tenacity of attention. HUMET®-R had such an optimizing, balancing effect on them that outstanding performance could be maintained despite continuous intense physical training stress.
- c) In hair loss attributable to trace element deficiency, it promoted the regeneration and growth of hair while contributing to a better subjective mental and physical condition.
- d) HUMET®-R is a non-specific adjuvant agent acting through increasing overall stress resistance. As such it could considerably improve the life quality of the aged, but also of patients suffering from neoplastic diseases by reducing pains and the need for painkillers, so helped restoring a more active life.
- e) In children, it normalized iron-deficiency anemia and therapy-resistant chronic eczema, restored lost appetite and mental vigor.

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Oncology and Radiology Science Research Institute
of the Ukraine Ministry of Health

Test Report Excerpts
on the clinical testing of HUMET-R syrup

Paediatric oncology
Scientific research Division

Division Head
Candidate in Medical Sciences

G. I. Klimnyuk

Ukraine Oncology and Radiology Science Research Institute

Test Report

Topic: "The application of HUMET-R product on patients suffering from malignant lymphoma in combination with cytostatic therapy"

Test conducted by Dr. Sz. Szivkovics, Research Executive and Doctor of Medicine, Head of the Department of Tumourous Diseases

Department of Tumourous Diseases
Kiev, 1997

TRACE ELEMENT SUPPLEMENT ROBORANT

Registration No.: OSZUI-430/1993

It has been a known fact of medicine for long that some elements of the periodic table are indispensable for living organisms and the human organism, in particular.

Every organism needs to receive the necessary dosage of trace elements to lead a normal active life. Our nutrition today is often unable to supply the necessary dosage of trace elements and efforts are needed to supplement them. Recent studies reveal that the application of complex products containing micro and macro-elements are significantly more efficient than monotherapy. Humet-R roborant syrup manufactured by Horizon-Multiplan Rt. meets these special requirements.

Humet-R syrup's main feature lies in its ability to tie the ten most essential trace elements to humic acids, known to be natural carriers in the human organism. Humic acids in the product contain 16 different amino-acids: their presence is supported by amino-acid analysis.

HUMET-R SYRUP COMPOSITION

10 ml substance contains 75 mg humic acids, 36 mg potassium, 15 mg magnesium, 14 mg iron, 10 mg zinc, 3 mg manganese, 2 mg copper, 0.5 mg vanadium, 0.2 mg cobalt, 0.17 molybdenum, 0.12 selenium and fixing.

DOSAGE

Added once a day after central meal, well shaken:

- 10 ml to adults,
- 5 ml to children of less than 40 kg in weight

Syrup diluted in 100-200 ml of water or fruit juice.

HUMET-R was prescribed for 40 patients on the Department of Tumourous Diseases. 20 patients were suffering from diagnosed lymphogranulomatosis. 7 patients in Stadium IV-B (35%), 3 patients in Stadium III-B (15%) and 4 patients in Stadium II-B (20%). For the remaining 6 patients, HUMET-R was prescribed for the treatment of recurring dissemination (skeleton and-locomotive system, lung and liver damage). As the characteristics of patients treated with HUMET-R would suggest, the therapy was applied on the most acute patient group in view of the fact that the presence of intoxication symptoms (fever higher than 38 degree centigrade, strong ephidrosis, a loss of weight of more than 10 percent in six months, the involvement of organs and tissues in neoplasm) makes efficient treatment of these patients extremely difficult. Before treated with HUMET-R, all patients were subjected to chemotherapy or radiotherapy. Strong intoxication symptoms (nausea, vomituration, general weakness) are known to accompany cytostatic therapy for most patients. During the application of HUMET-R a deterioration in general conditions (nausea, emesis, asitia) was observed in one patient (Patient R) only, which – according to the attending physician – was attributable to the use of HUMET-R. The treatment was thus abandoned on the fourth day of the trial. For the other 20 patients participating in the trial, Non-Hodgkin lymphoma was diagnosed. For 6 patients the degree of malignancy was moderate (30%), while a highly malignant Non-Hodgkin lymphoma was diagnosed for the other 14 patients.

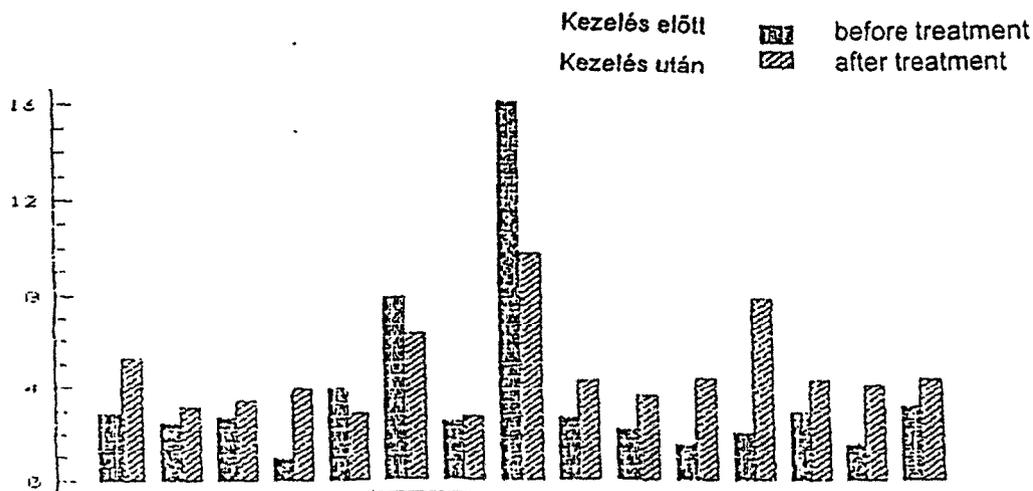
We know that Non-Hodgkin lymphoma – as a heterogeneous group of diseases – is causing a huge problem in today's onko-haematology in view of its treatment. 19 patients in this group received HUMET-R in combination with poly-chemotherapy. Remote τ -therapy was used during the previous cytostatic treatment for 8 patients (40%) only. One of our patients took HUMET-R in combination with radiotherapy.

HUMET-R improved the general conditions of all patients involved (less fatigue, and reduced nausea). HUMET-R intake had to be abandoned in one case only as this patient showed intolerance to the radiation of lymphatic glands at the epigastrium.

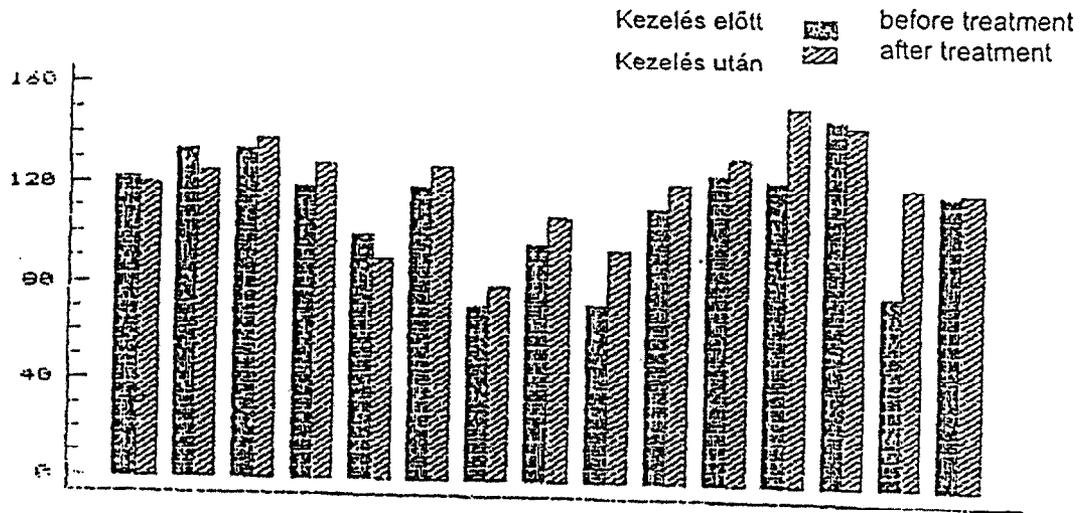
One of the patients, at his own request, received two HUMET-R treatments as the product completely stopped intoxication symptoms.

Following is a presentation of the dynamic changes in measured leukocyte (white blood cell) and haemoglobin factors of patients treated with HUMET-R. The treatment was combined with cytostatic therapy.

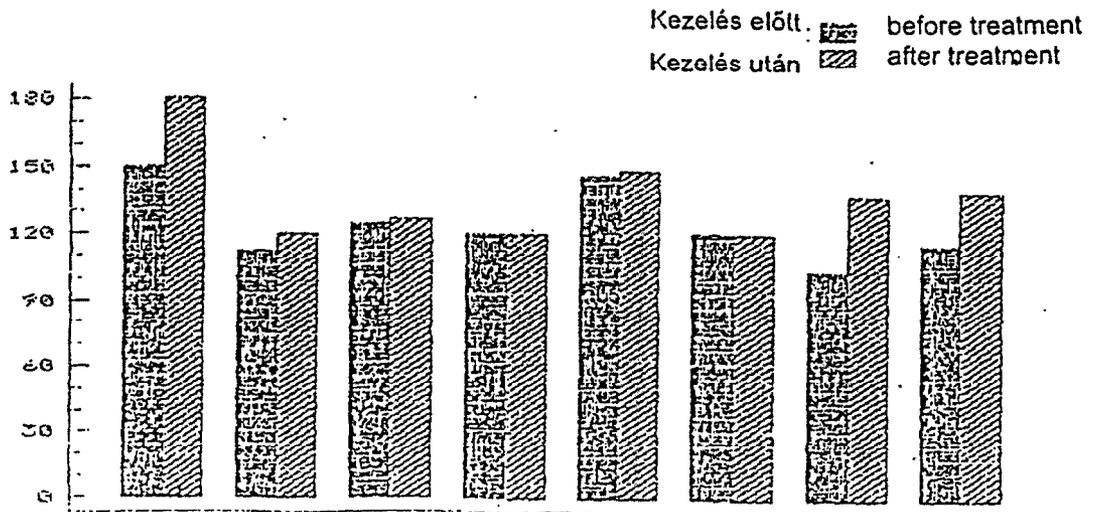
Leukocyte factor dynamics in patients suffering from lymphogranulomatosis (before and after treatment)



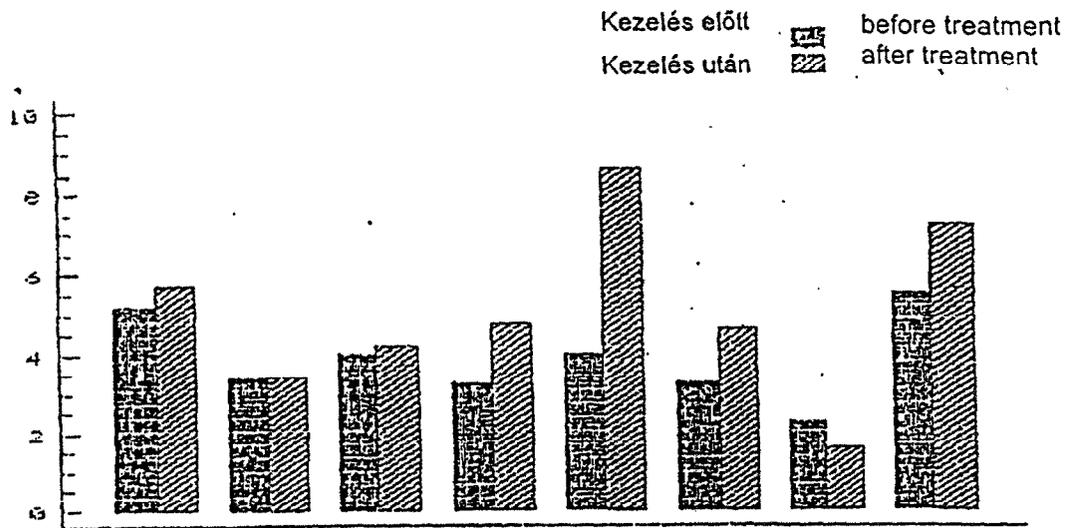
Haemoglobin quantity factor dynamics in patients suffering from lymphogranulomathosis (before and after treatment)



Haemoglobin quantity factor dynamics in patients suffering from Non-Hogdkin lymphoma (before and after treatment)

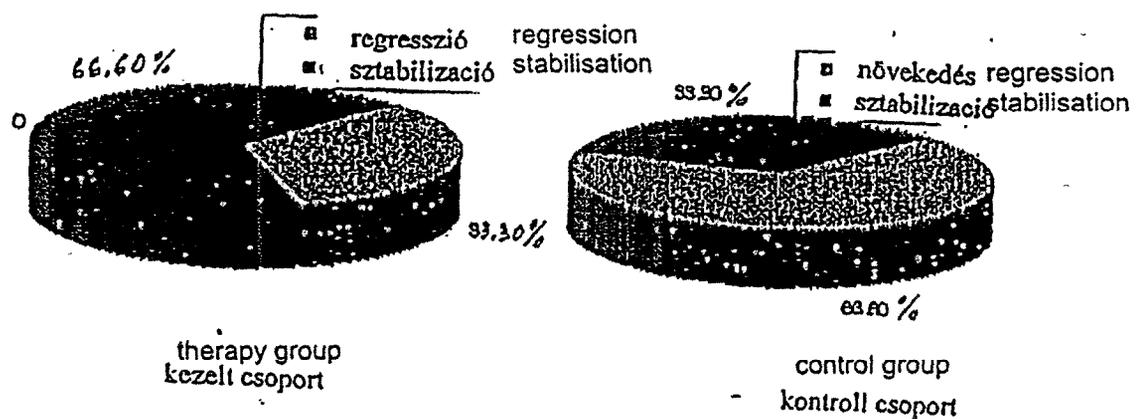


*Leukocyte quantity factor dynamics in patients
suffering from Non-Hodgkin lymphoma (before and after treatment)*



In view of the clinical test results and the laboratory diagrams the conclusion can be drawn that the application of HUMET-R is a reasonable therapy option in the treatment of patients suffering from Non- Hodgkin lymphoma and lymphogranulomathosis, in combination with cytostatic therapy. Lengthier and more detailed studies will be needed to determine the effects of the syrup in relation to the patients' remission time and chances of survival laying the foundations of studies conducted to determine the product's indications and counter-indications in the medical treatment of cancerous patients.

Lung cancer dynamics after treatment



No negative effects of HUMET-R of any kind were observed during the clinical and laboratory tests in relation to the organism of patients suffering from oncologic diseases of the skeleton and locomotive system and skin tumour. Patients with a tumour who underwent surgical intervention, radio- or chemotherapy were more tolerant to the therapy and the post-traumatic period when using HUMET-R.

HUMET és Kereskedelmi, Kutatási és Fejlesztési RT
(HUMET and Trade, Research and Development Company Limited by Shares)
Budapest, 1121 Konkoly Thege u. 29-33.

Dr. Éva Sallay

REPORT

HUMET®-R **OPEN-LABELLED PROSPECTIVE CLINICAL** **RESEARCH ON VOLUNTEERS EXPOSED TO** **LEAD**

AJKA
1998

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Summary

Title:

Report on the test identified as open labelled prospective clinical trial of the HUMET-R syrup on volunteers exposed to lead.

Place:

Ajka Kristály, Factory Health Service, Surgery, 8400 Ajka, Alkotmány u. 4.

Purpose:

The purpose of the trial was to study whether the intake of a daily dose of 10 ml of Humet-R would accelerate the excretion of harmful heavy metals (Pb) that have accumulated in organisms exposed to high dose of lead.

Field of use:

Intensive lead exposure.

No. of patients involved:

The trial was carried out on 60 volunteers, whose serum lead level had exceeded 1 $\mu\text{mol/l}$.

Test sample

The trial was carried out using the HUMET-R that is sold in the market.

Dosage:

Volunteers received 10 ml of HUMET-R continually over a period of 12 weeks. 22 volunteers had to be moved from their previous workplaces due to high blood lead level, but they continued to participate in the treatment and they were also involved in the control examinations.

Examined parameters:

Serum blood, routine laboratory tests, liver function and kidney examinations, routine urine examination.

Results:

The trial has shown that the intake of a daily dose of 10 ml was not as efficient as in the case of an earlier test (involving 35 patients who took a daily dose of 20 ml), in which the drop in blood lead level was significant after even a 6-week treatment – the rate of reduction was $1.86 - 1.46 = 0.40 \mu\text{mol/dm}^3$. The analysis of the data relating to 58 patients has shown that the change became significant only by the end of the 12th week, compared to pre-treatment figures.

Transferrin increased by 4-5% on average.

Serum iron did not change in a statistically significant extent during the treatment.

In the persons who were excluded from lead exposure during the trial, the mean value of Se Fe dropped by 6.3%, a statistically insignificant rate.

The value of RBC free protoporphyrin measured at 12 weeks was significantly lower than the pre-treatment level, while the difference was significant at the closing examination. In the patients excluded from exposure the mean value dropped, but to an extent that was statistically insignificant.

Side effects

Side effects were manifested in two volunteers (one gastrointestinal and one dermal). Both volunteers stopped the therapy.

1. Introduction

Microelements function partly as particles of enzymes and partly as their activators. The lack of microelements or the dominance of their antagonists may influence the functioning of certain enzymes adversely, thereby causing deficiency disease or symptoms associated with the morbid functioning of enzymes.

The organism's need for microelements can be satisfied through diversified nutrition in the case of normal absorption. However, the microelement content of human food has changed both in terms of quality and quantity, because they no longer can be found in the soil and so in foods originating from plants and animals. The problem is made even more complex if we take into account that even microelements that were taken into the organism in sufficient quantity are not absorbed fully. As a result, it is a common trend that regular trace element intake in quality and quantities that satisfy the needs is provided irrespective of the food intake.

Based on the results of the latest research, several decades of experience in veterinary medicine and toxicological and other examinations the researchers of HUMET RT have developed a natural carrier substance that provides the organism with the added, physiologically most important micro and macro elements in sufficient quantities, and also facilitates their absorption. This carrier substance obtained from nature consists of a blend of humic acids (grey, brown humic acids), fulvic acid and their metabolites. Humic acids are mixtures of active biopolymers of diverse molecular weights. These compounds – that do exist and have their role in the human organism – are important, because of the chelating characteristic of their variable functional nuclei.

Humic acids have an affinity toward metal ions that resembles the activity of transport proteins of the human organism. This means that the binding strength series of proteins is identical with the binding strength series of humic acids.

HUMET R contains a huge amount of iron, which is a fundamental component of oxygen-transporting haemoglobin, electron-carrying cytochromes and the functional group of myoglobins. Iron deficiency produces clinical symptoms (fatigue, headache, inflammation of the oral mucosa, gingivitis and anorexia etc.). Chronic deficiency might lead to the development of hypochromic anaemia accompanied by microcytemia and myeloid hyperplasia that hardly contains any haemosiderin. Anaemia results in reduced intellectual and physical capacity of the organism.

Macro and microelements do have an influence on the absorption and excretion of each other. Iron take up by the organism is greatly influenced by the presence or lack of microelements, at the same time humic acid intake will facilitate the discharge of lead.

The basic substance of the HUMET®-R syrup is a colloid solution containing a blend of humic acids, it is therefore the optimal carrier substance because of its variable functional groups:

- it contains the trace elements in a biochemical structure – chelated form – highly resembling the transport proteins of the organism, therefore facilitates their absorption in a favourable form;
- as evidenced by international experience, it binds macro and microelements added to it in the recommended daily allowance (RDA) with variable strength and so ensures that always the needed volume is absorbed;

- it removes from the organism any undesired, often harmful elements that found their way into the organism, such as lead, cadmium, by binding them strongly to humic acid.

Heavy metal pollution in countries with advanced industries is a general phenomenon. Especially people working in certain industries (e.g. metallurgy, paint industry, glass manufacturing and grinding) are exposed to high doses of pollution. Employees working in such circumstances are protected against grave intoxication in the developed countries by organising regular medical checks and if the heavy metal loading of their organisms exceeds the critical level, they are temporarily removed from their former workplaces.

Heavy metals that got into the organism and were absorbed are strongly bound to sulfhydryl groups that can be found in tissues and form a prosthetic enzyme group and hinder their functioning. Chronic heavy metal intoxication and lead poisoning produce different and versatile clinical symptoms.

Symptoms of chronic lead poisoning may include disturbance in ossification, liver function disturbance, gastrointestinal complaints, e.g. anorexia, renal injury, problems of the nervous system, encephalopathy, depression, hallucination, epileptic symptoms, psychic alterations, agitation, insomnia, injury of blood-forming organs, anaemia, high blood pressure, effects on the organs of locomotion, muscular weakness, articular pain, impotence in men and sterility in women. Children are more sensitive to high blood-lead level.

A research carried out by Mr. I. Sarudy and co-workers with the ^{203}Hg isotope on pigs found that humic acid intensified the discharge of the isotope both in the faeces and the urine.

Mr. Hudák et al. studied the effect of a syrup containing humic acid on 15 male patients exposed to cadmium, and found that after a six-week treatment the serum Cd level was significantly reduced while level of Cd discharge in the urine increased. This was accompanied by improved liver function and urine parameters in the patients examined.

In an earlier test carried out by Mr. Flórián and co-workers pursuant to an identical protocol on volunteers with a blood lead levels of 1-2.99 $\mu\text{mol/l}$, who nevertheless considered themselves healthy, these volunteers took the HUMET-R syrup in 20 ml/day doses. Volunteers were treated for a period of six weeks. Laboratory examinations were held following therapy for 3 weeks and 6 weeks, respectively. Very significant reduction in blood-lead level ($p < 0.01$) was recorded by the end of the sixth week in the treated group. Compared to the control group the difference was significant ($p < 0.05$).

2. Purpose of the study

Since, because of the relatively high Selenium content of the preparation (12.5 $\mu\text{g/ml}$), it may not be given in doses of 20 ml without continual medical supervision, we wanted to find out whether this lead-reduction effect would be manifested if a lower dose of 10 ml/day – as permitted by the National Pharmaceutical Institute (OGYI) – is given. In other words, we wanted to ascertain that when taken in a lower dosage the product would

– through its puffer action – accelerate the discharge of harmful heavy metals that have accumulated in organisms exposed to high dose of lead.
 During the study programme eventual undesired symptoms and side effects were also evaluated.

3. Type of study

Open-labelled, control group trial carried out within the framework of outpatient care.

Places of examination

Sponsor	HORIZON-MULTIPLAN Kft. 1121 Budapest, Konkoly Thege Miklós út 29-33. Phone: 160-1828 Fax: 160-3704
Clinical phase	Ajka Kristály Üzemorvosi Rendelő (Ajka Crystal Factory, Factory Medical Service, Surgery) 8400 Ajka, Alkotmány u. 4. Research manager: Dr. Éva Sallay head physician
Laboratory tests	Hospital Laboratory, Sümeg Kompanik Zsófia u. 6. 8330
Blood lead assay	State Public Hygiene and Medical Officer's Service (ÁNTSZ) of Veszprém County (blood lead determination) 8200 Veszprém, József Attila út 36. Phone: 06-88-424-866, fax: 06-86-428-686 Person responsible for the topic: dr. Mrs. Gy. Koppa Responsible research manager; dr. László Budosó Deputy Medical Officer of Veszprém County

4. The test product

4.1 The sample

The test product used in the trial was the preparation produced and distributed by HUMET RT. (formerly called as HORIZON-MULTIPLAN RT.).

HUMET®-R syrup reg. no.: OGYI-340/1993
 Lot number of the sample: ????????????????

The HUMET®-R roborant preparation is a humic acid extract produced as the result of a special treatment, supplemented (doped) with ten types of micro and macro elements, with fruit syrup flavour. The recommended daily dose for adults is 10 ml, which contains the macro and microelement quantity set out in WHO recommendations.

The 300 ml unit pack of the product contains 2.25 g humic acid, 1.10 g Potassium, 450 mg Magnesium, 420 mg Iron, 300 mg Zinc, 90 mg Manganese, 60 mg Copper,

15 mg Vanadium, 6 mg Cobalt, 5.25 mg Molybdenum and 3.75 mg Selenium mixed in an orange-flavoured syrup.

4.2 Administration of the preparation

The volunteers involved in the research programme took the preparation in a daily dose of 10 ml in their homes, in accordance with the specifications, at the time of their main meal.

5. Ethical issues

Only volunteering individuals were involved in the trial.

The volunteers reporting for participation in the trial were informed verbally and in writing about the purpose, the process and the duration of the study. The information for volunteers described the expected effect of the test products in detail as well as the eventual side effects, the frequency and content of clinical examinations. The information paper described the obligations to be assumed when volunteering and the right of volunteers to request – even verbally – the stopping of the trial at any time, without any consequences.

The participants signed the Volunteer's Statement in confirmation of having been properly informed and their agreement to these terms.

The trial was conducted in accordance with the protocol approved earlier by the local Ethical Committee. (Annex III.)

6. Departures from the protocol

After the trial process was started the programme was modified compared to the original protocol. By the end of the sixth week a lead assay not planned before was held in order to make the tracing of the process of changing possible. (Annex IV.).

Workers, whose blood lead level exceeded the critical value were excluded from work right at the beginning. We made exceptions in the case of three patients with levels of 2.6 $\mu\text{mol/l}$ and one patient with 2.7 $\mu\text{mol/l}$, for whom we agreed to wait up to the first control examination. The laboratory had indicated a 20% standard deviation in the accuracy of lead assay and the above values fell within that range. Postponement of their exclusion from work was carried out in the case of key employees, whose work was crucial for the operation of the company and subject to informing them.

7. Selection of volunteers

7.1 Criteria for participation

Volunteering workers of the Ajka Crystal Factory aged 18-60 of both sexes, who had been exposed continually to high dose of lead prior to starting the trial and whose blood lead level measured during obligatory blood lead control examinations held every six months was $\geq 1.0 \mu\text{mol/l}$.

60 volunteers were selected to participate in the study.

Volunteers, whose blood lead levels exceeded 2.4 $\mu\text{mol/l}$ by the end of the third week were removed from their workplace and employed in a less risky job, until their blood level dropped below 2.5 $\mu\text{mol/l}$.

In the case of young female workers the critical threshold was 1.5 $\mu\text{mol/l}$.

7.2 Reasons for exclusion

- suspected lead poisoning (necessity of EDTA treatment),
- pregnancy, breast-feeding,
- kidney, liver and heart failure,
- circulatory and/or respiratory problems,
- blood clotting disturbance,
- disease of the central nervous system or psychiatric illness,
- acute allergic illness,
- diabetes mellitus,
- permanent medication (except for oral contraception),
- abuse of alcohol and/or drugs.

7.3 Drop out

Volunteers who did not wish to continue the treatment were regarded as drop-outs just as those who produced symptoms of intercurrent disease, serious side-effects or intolerance.

In the course of this trial, two persons dropped out:

1. 03.PJ. For two days following the starting of the trial he/she perceived vomit and gas-forming. Level of severity – mild, no intervention was needed. It developed uninterruptedly and without complications. The treatment was stopped, the undesired phenomenon is likely connected to taking the product.

2. 31.UE. In the last two weeks of the protocol tiny, itching wheal covered the whole body. Level of severity – mild, no intervention was needed. It developed uninterruptedly and passed without complications. It is possible that the undesired phenomenon is linked to the taking of the product. During participation in the trial the parameters of the volunteer never deviated significantly from the average parameters of the group (see the last lines of the Tables marked ..b).

8. Duration of the trial:

Starting date of the test:	25.02.1998.
End of the test:	30.06.1998.

9. Trial procedure:

The duration of the trial (the treatment period of one patient) was 12 weeks.

The volunteering glass factory workers, who had participated in the obligatory serum lead screening examinations and met the criteria for participation reported for the trial in the factory medical officer's surgery.

On the first day of the research programme history was taken, physical check-up, ECG, measuring of blood pressure and heart rate and laboratory tests were performed.

The volunteers involved in the trial were given the HUMET®-R syrup in a quantity sufficient for a treatment of three weeks, of which they took 1x10 ml syrup per day after the main meal in accordance with the instructions on administration.

Control examinations were held on the 42nd and the 84th (± 3 days) days.

The volunteers appearing for control examination participated in laboratory tests, which – according to the protocol – comprised the following examinations:

9.1 Physical check-up

Examination	Method
ECG	MR-11
Blood pressure	RR
Pulse	Feeling

9.2 Laboratory tests

Examination	Method	Normal range
haematology:	COBAS MICROS-Roche automatic analyser	
WBC		4-9 x 10 ³
Segm.		40-70%
Lymph.		20-45%
Eos.		1-6%
St.		1-2%
Mo.		1-2%
RBC		4-5.5 x 10 ⁶
Hg.		120-170 g/l
HTC		38.0-50.0%
MCV		85-100 fl
MCH		28-32 pg
MCHC		320-360 g/l
Thr.		150-400 x 1000/ml
Sedimentation		1-2 mm/h

Chemical examinations:		
- se Na	Referenzmethode (Flammenphotometrie)	135-145 mmol/l
- se K	"	3.5-4.8 mmol/l
- BUN	UV test (Urease-GLDH)	2-10 mmol/l
- se creatinin	Jaffé (mit enteiweissung)	45-106 µmol/l
- se bi.	DPD	4-21 µmol/l
- blood sugar	Hexokinase	3.3-5.9 mmol/l
- ALP	DGKC 37 °C	98-279 U/l
- SGOT	IFCC (ohne pyridoxalphosphat) 37 °C	0-47 U/l
- SGPT	IFCC (ohne pyridoxalphosphat) 37 °C	0-49 U/l
- LDH	DGKC 37 °C	230-460 U/l
- Gamma-GT	SZASZ 37 °C	
- Se cholesterol	CHOD-PAP (Endproduct)	2.9 -5.7 mmol/l
- Se triglyceride	GPO-PAP	0.8-1.9 mmol/l
- Se Fe	Ferrozin (ohne enteiweissung)	12.5-25 µmol/mol
- Se-transferrin	Nephelometrie	2-4 g/l
blood Pb,	Perkin Elmer 3000 AAS	Umol/dm ³
ZnPP	Free PP	µmol/mol
Urine analysis:	ELU Test-URI CONT (vendor 77 Elektronika)	
- density,	Weight measurement	1015-1025 g/l
- pH,	ELU Test-URI CONT (vendor 77 Elektronika)	4-10
- protein,	Biuret (ohne Probe-Leerwort)	-
- sugar,	ELU Test-URI CONT (vendor 77 Elektronika)	-
- acetone,	ELU Test-URI CONT (vendor 77 Elektronika)	-
- UBG,	ELU Test-URI CONT (vendor 77 Elektronika)	-
- sediment.	Microscope	-

10. Monitoring of side effects

All objective and subjective side effects were monitored and recorded on the individual data sheets. Whenever serious side effects or unexpected effects were realised, the volunteer was excluded from the examination. (See page 9 Drop out, patients no. 03 and 31.)

11. Results

11.1 Demographic numbers

The trial programme was completed by 58 of the volunteers. Of the 58 volunteers thirty-six carried on working at their former workplaces, while twenty-two volunteers were re-located due to their high blood lead levels, but these volunteers continued the treatment and participated in the control examinations, too.

When evaluating the results, statistical tests were carried out on the parameters of all the 58 volunteers, whose data were evaluated, while statistical tests were performed separately on the parameters of group "a" consisting of those continually working at the same workplace and group "b" of those re-located.

In respect of their physical status (bodyweight, height, blood pressure, pulse rate) the two groups did not differ from each other (Statistics page 3).

History revealed noteworthy disease in seven volunteers (Crohn's disease, myoma uteri, TBC, pancreatitis, ulcus ventriculi, pneumonia, hypertension + cholecystectomy), each once.

Five persons reported hypersensitivity (bee sting, sulphonamide, metal, aminopyrine, nylon), each once. (Statistics, Demography.)

ECG deviation was realised in one volunteer only.

11.2 Evaluation of laboratory results

11.2.1 Pre-selection examinations

Laboratory I.

The specific parameters are shown in Table 2. In the consolidated data only mean RBC free protoporphyrin exceeded the given normal upper limit significantly.

In the groups defined by the level of exposure mean protoporphyrin was also higher than the normal limit value, while in group "b" it was significantly higher than in group "a" (based on one and two tailed t-tests). So the two groups started the trial with different base levels. Blood lead level was also significantly higher in group "b" (2.6 ± 0.65) than in group "a" and it also exceeded the permitted limit value, although not significantly. In addition to this, white blood cell count and St % were also higher in group "b" than in group "a", although these parameters did not deviate significantly from the upper limit.

Laboratory II.

The parameter details can be seen in Table 3. Mean values never exceed the permitted limits.

If volunteers are divided into groups according to the duration of exposure – despite the fact that mean values were in the range of normal values except for triglycerides (they were somewhat higher) – the mean ALP and SGOT were significantly higher in the “b” group than in the “a” group.

Laboratory III.

Table 4 shows the data obtained from urine analysis at the time for selecting the volunteers. The average value of density and pH did not deviate from the normal parameter. The same applies to the values produced in the broken up groups. The only pathological protein case (34) occurred in group “b”, while the pathological sugar + acetone case (27) was found in group “a”. There was one excessive UBG in group “a” (21) and group “b” (5), respectively.

11.2.2 Control examinations

Laboratory IV.

The results of control laboratory examinations performed in the 6th and 12th weeks of treatment can be seen in Table 5. In the consolidated records mean blood lead levels were within the normal range in both cases, while RBC free protoporphyrin was significantly higher ($253 \pm 24.6 \mu\text{mol}/\text{dm}^3$, and $244.5 \pm 24.2 \mu\text{mol}/\text{mol}$).

The same is true for the average values of group “a”. In group “b” however the mean blood lead level exceeded the limit value, although not significantly ($2.5 \pm 0.17 \mu\text{mol}/\text{dm}^3$). The differences between the two groups’ mean values were significant on both occasions, and the values of group “b” were higher.

11.2.3 Closing examinations

Laboratory I.

The detailed parameters can be seen in Table 6 (Lab V). The mean values never exceeded the normal limits. The t-tests – when applied – showed significant deviation compared to initial values in the mean values of RBC (some reduction), haemoglobin (increase), MCH (increase), MCHC (increase), blood lead level (reduction), RBC free protoporphyrin (reduction) and St % (increase).

In group “a” the mean value of free protoporphyrin ($210.1 \pm 23.5 \mu\text{mol}/\text{mol}$) exceeded the limit value significantly, while that of ST % it exceeded it slightly ($2.3 \pm 0.4\%$). In comparison with initial values, significant change was observed in RBC (some reduction), MCH (some increase), blood lead level (reduction), free protoporphyrin (reduction) and St % (increase).

In group "b" the free protoporphyrin was significantly higher ($275 \pm 47.6 \mu\text{mol/mol}$), while the mean value of St % was somewhat higher ($2.2 \pm 0.4\%$) than the laboratory-determined limit values. In this group there was significant change from initial values in mean haemoglobin (increase), MCH (increase), MCHC (increase) and blood lead level (reduction). The average values of group "b" were significantly higher than those of group "a" in blood lead level and free RBC protoporphyrin.

Laboratory II.

Detailed parameters can be seen in Table 7 (Lab VI). The mean values of these laboratory parameters never differed from laboratory normal values. The t-test has shown the following significant differences from the initial mean values: Se Na (reduction), Se K (reduction), BUN (some reduction), ALP (some increase), SGOT (mild reduction), SGPT (reduction) and cholesterol (some reduction).

In group "a" the mean values were also within the normal range. Significantly deviated from initial values the Se Na (reduction), Se K (reduction), ALP (some increase), SGPT (reduction) and cholesterol (some reduction) values.

In group "b" the mean values – except for triglycerides (not significantly higher, 2.3 ± 0.7) – were in the normal range. Significantly differed from initial mean values the Se Na (reduction), Se K (reduction), Se creatinin (increase), SGOT (reduction), SGPT (reduction) values. There was no significant difference between the average values of the two groups.

Laboratory III.

The closing results of the urine analysis are shown in Table 8 (Lab VII.). Similarly to initial status, the mean value of density and pH did not differ from normal levels. However the mean density value of the closing examination was significantly higher than the initial value. The same can be said about the group parameters. The only pathological protein (34) in group "b" remained and another was perceived in group "a" (53), while the pathological sugar + acetone (27) in group "a" also remained. No increase in UBG was detected this time.

12. Evaluation of potency examinations

12.1 Development of blood lead level during the trial programme

Table 9 shows the development of the main statistics of the parameters.

It was realised after the statistical processing of data that 4 parameters were indicated with the wrong value by mistake and this was not realised even during the check-reading. Therefore, all the laboratory results were checked once more, but no further difference was found.

Based on the modified blood lead levels the calculations were repeated, but in fact the results were not affected. The new tables are attached to the table of the statistical report as an appendix, after Table 11.

The mean values have a decreasing tendency, while median and standard deviation levels were reducing also. In the consolidated group just as in the group of volunteers who were exposed to lead all through the trial the variation coefficient also reduced somewhat and this is an indication that the group followed converging tendencies.

By the end of the therapy the mean blood lead level drop in the whole group of volunteers was by $0.18 \mu\text{mol}/\text{dm}^3$ (8.4%), while in the group exposed to lead all through the trial the reduction was by $0.12 \mu\text{mol}/\text{dm}^3$ (6.5%). In the group removed from exposure it was by 0.26 units (10.6%). The rate of reduction was significant in all these cases.

In the whole group of volunteers and in group "a" reduction was significant already at the second control examination (12th week), while in persons removed from exposure (group "b") it became significant only by the end of the treatment period.

In respect of distribution by sexes, there was no difference between the two groups as reduction reached a significant rate at the closing examination in both groups.

In women exposed to lead all through the trial the difference compared to base values was significant, $p < 0.02$ and 0.012 , by the 12th week and at the closing examination. The difference was $0.10 \mu\text{mol}/\text{l}$ and $0.14 \mu\text{mol}/\text{l}$. In women removed from exposure, due to the low number of elements, the difference compared to base values was not significantly lower than before the treatment, although the average reduction rate was $0.18 \mu\text{mol}/\text{l}$.

In men continually exposed to lead the blood lead level dropped significantly only by the time of the closing examination ($p < 0.04$, the reduction was by $0.11 \mu\text{mol}/\text{dm}^3$). The drop in blood lead level in men removed from exposure was by $0.28 \mu\text{mol}/\text{dm}^3$ at the time of the closing examination compared to initial values, which is a highly significant change.

The process of change in blood lead level is shown in Figure 1. The curves indicate a similar, monotonous reduction.

Based on the mean values and standard deviation of the differences of individual results prior to and after the treatment, we have established the confidence interval of the averages. Then we defined the percentages of patients that belong to average change, lower or higher categories. Naturally this breakdown is not absolutely precise, since difference (change) is determined in an accuracy level up to one decimal, but this applies to all the groups and so it is suitable for breaking the volunteers down to such categories. The changing capability of each group is shown in the following table:

	Rate of reduction		
	lower than average	average	higher than average
Altogether	24.1%	39.7%	36.2%
group a	47.2%	22.2%	27.8%
group b	18.2%	54.5%	27.3%

In group "a" changes are typically lower than the average, while in group "b" they are typically just about average.

12.2 Development of free RBC protoporphyrin during the research programme

Table 10 shows the key statistics of this indicator. Average values here also show a dropping tendency, while the median value also decreases. Standard deviation however increased, especially in group "b". Thus, the variation coefficient also shows an increasing tendency, which indicates significantly differing reactions of each person. The rate of reduction in average value in the whole group was 26.0 $\mu\text{mol/mol}$ (10.0%), in the group exposed to lead all through the programme it was - 30.0 units (12.5%), while in the group of patients removed from exposure it was 19.6 units (6.7%). In the former two groups reduction reached a significant level by the end of the therapy, moreover statistically significant change was realised even before the end, while in group "b" the change was statistically non-significant.

The process is indicated in Figure 2. The bending of the curves shows a similar, monotonous reduction.

Similarly to the above section we broke up the group of volunteers into three categories according to their changing rates. The table below shows the changing capability of each group:

Rate of reduction	lower than average	average	higher than average
	Altogether	34.5%	32.8%
group a	33.3%	36.1%	30.6%
group b	22.7%	59.1%	18.2%

In this case the distribution of group "a" is nearly even, while group "b" shows a more uniform changing pattern, in which nearly average reductions dominate.

12.3 Development of Se Fe and transferrin level in the course of the research

The key statistics taken at the time of selection and closing are shown in Table 11. It is clear in the case of both indicators that no statistically significant change can be perceived during the treatment period. Mention should be made of the - statistically insignificant - drop in the mean value of Se Fe by 6.3% in the persons removed from exposure.

The process is demonstrated in Figure 3. Each group can boast of changes of different rates, but - since the change was statistically insignificant - these changes cannot be evaluated.

When breaking down the group of volunteers according to changes in individual results, in group "a" the categories "reduced-no change", while in group "b" the categories "no change-increased" have a higher frequency. This is seemingly contradictory to the above curve, which indicates the difference between the two indicators (change in mean values and the average of individual differences).

Se Fe			
	reduced	no change	increased
Altogether	38.2%	23.6%	38.2%
group a	35.3%	35.3%	29.4%
group b	28.6%	38.1%	33.3%

An average increase by 4-5% has been realised in transferrin. The higher value was measured in persons exposed to lead up to the end, although the rate of change cannot be regarded as statistically significant even in this group. The groups seem to have behaved in a similar pattern (Figure 4).

Distribution by changes:

Transferrin			
	reduced	no change	increased
Altogether	41.1%	17.9%	41.1%
group a	35.3%	23.5%	41.2%
group b	31.8%	36.4%	31.8%

13. Side effects

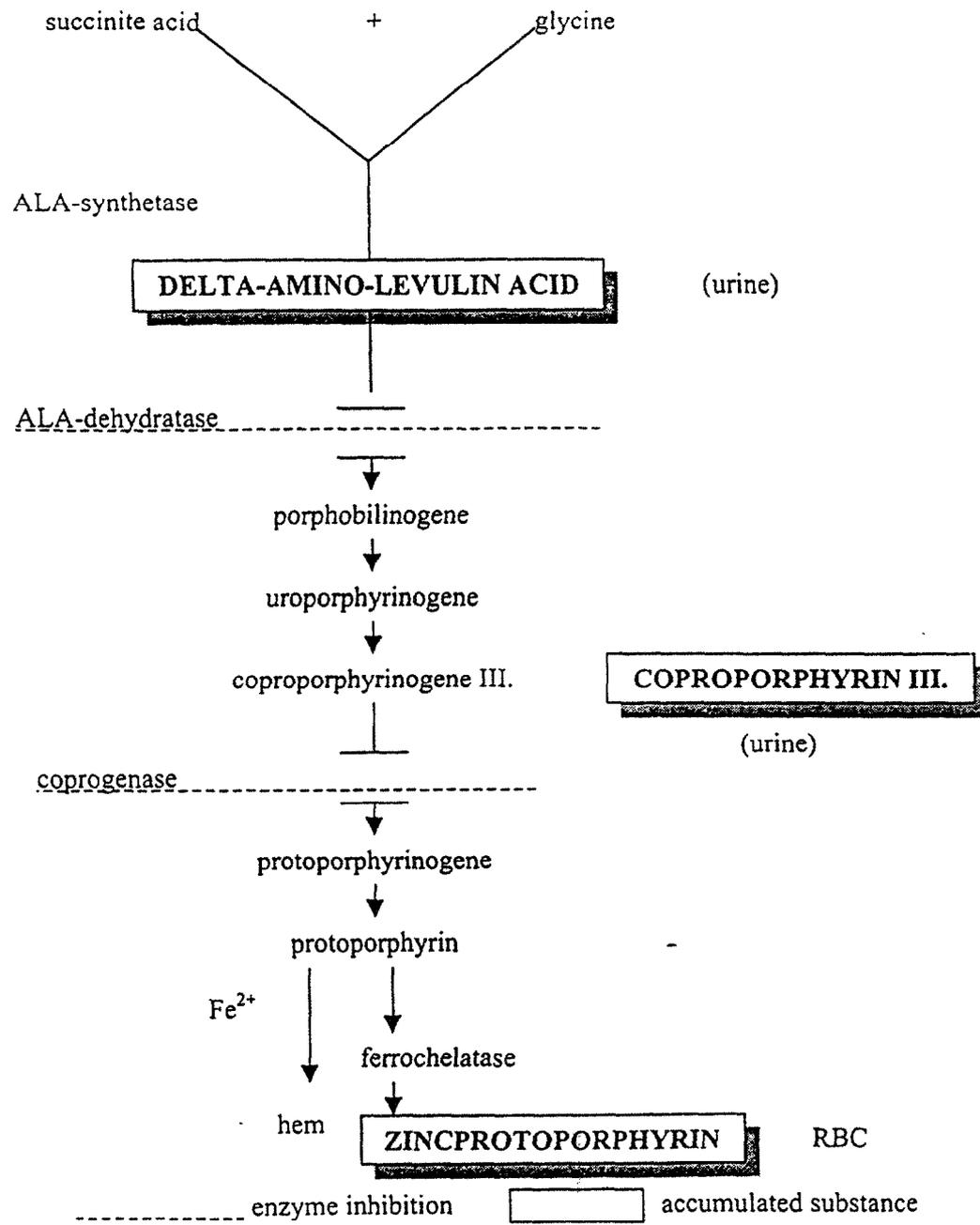
Of the 60 patients involved in the trial no-one stopped the treatment on their own decision. The therapy had to be stopped in the case of two volunteers because of intolerance and intercurrent disease.

(See page 9 section 7.3, Drop out of patients no. 03 and 31.)

14. Evaluation

The two-year research involving sixty persons represents a headcount that allows for the use of the two-sample one tailed and two tailed t-tests. Consequently, certain conclusions can be drawn. The selection of participants and professional duties were carried out strictly in accordance with the given protocol, thus any subjective opinion could be ruled out. The research programme was carried out to the end in accordance with the Declaration of Helsinki all along.

The key selection criteria included exposure and a minimum blood lead level of $1 \mu\text{mol}/\text{dm}^3$ as specified in the protocol. Re-location from the workplace was a necessity, as it was obligatory to stop exposure whenever the limit value defined by OMFI and ÁNTSZ was exceeded. Re-location took place based on Se lead level measurements carried out by accredited laboratories. The same way re-deployment took place when the measured parameter dropped below the normal limit.



Lead as a heavy metal, when it is taken up by the organism, gets deposited in parenchymal organs and the bone. It competes with Se Fe and causes iron deficiency anaemia in those exposed to lead. It might even damage the nervous system.

ZPP accumulation serves as a rough preliminary indicator. It has been observed that the increase of Se lead level follows that of the ZPP level by an interval of 3-5 months, although there are huge differences due to individual sensitivity. Those representing group "b" in the analysis must be mentioned here. Several years of observations and biological monitoring have shown that those, who were included in this group are of the "fast take-up" and "slow discharge" kind.

The higher WBC and St % found in Laboratory I can be considered as a reaction of the bone marrow.

The higher liver enzyme partial values measured in group "b" in Laboratory II also confirm the heavy charge on the parenchymal organ.

Closing laboratory examinations

Compared to initial values the higher Hgb, MCH, MCHC and St % increase indicate the regeneration of bone marrow – obviously because of the chelate-like lead binding capability of available iron and the peat in HUMET[®]-R.

The reduction of Se cholesterol seems also interesting and deserves to be followed up.

The same way the reduction of SGOT, SGPT level is also noteworthy. It might confirm that HUMET[®]-R by eliminating the lead deposited in the liver facilitates the normalisation of the enzyme level.

Development of Se lead

In the entire test population – considering 58 persons – Se lead dropped in 46 patients compared to the initial parameters, which indicates a 79.3% positive reaction to HUMET[®]-R.

This is backed up by significance calculation as well.

In those participating in group "a" HUMET[®]-R – after treatment for two months – brought about significant reduction in Se lead.

The aggressive reduction of ZPP can be observed in group "b", too, which could be an indication that the relieving of the organism (bone marrow) has started.

Development of Se Fe and transferrin

In group "b" there was no change – the higher level was more frequent.

These patients as individuals are more sensitive and belong to the group of people that cumulate better.

In their case probably higher Fe availability should be provided.
(The headcount of the group was 22 persons, which is insufficient for a safely reliable analysis.)

It seems reasonable to follow up on this metabolically more vulnerable group using a higher headcount and greater iron intake – if tolerable.

In an earlier research involving 35 patients who took a daily dose of 20 ml a significant reduction in blood lead was observed after 6-week treatment even. The rate of reduction was $1.86 = 0.40 \mu\text{mol}/\text{dm}^3$.

When a daily dosage of 10 ml was applied, the effectiveness was lower than that experienced earlier.

In the analysis of 58 patients' data the difference in blood level became significant compared to pre-treatment results only by the end of the 12th week of treatment.

Other laboratory findings have also confirmed the effectiveness of the product.

11-01-1999

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dr. Éva Sallay
head physician, research leader

.....
dr. Ilona Pazonyi
statistician

.....
dr. Árpád Király
quality manager

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16. Annexes

- I. Figures
- II. Statistical analysis
- III. Protocol
- IV. Protocol amendment
- V. Laboratory values and methods

Figure 1. Development of Se lead level during the trial ($\mu\text{mol}/\text{dm}^3$)

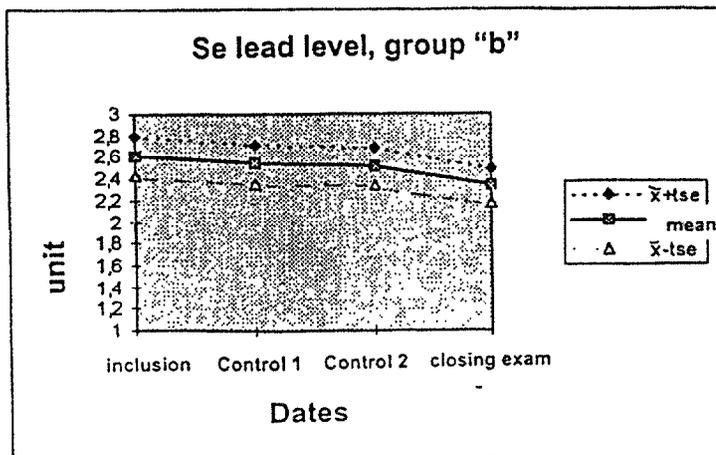
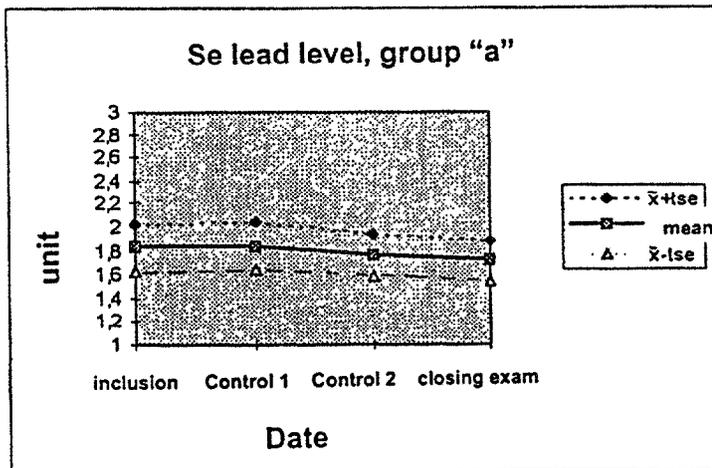
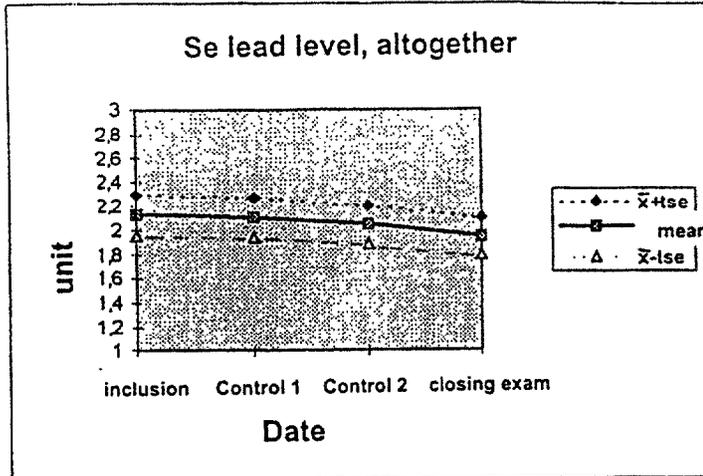


Figure 2. Development of free RBC protoporphyrin during the trial ($\mu\text{mol/mol}$)

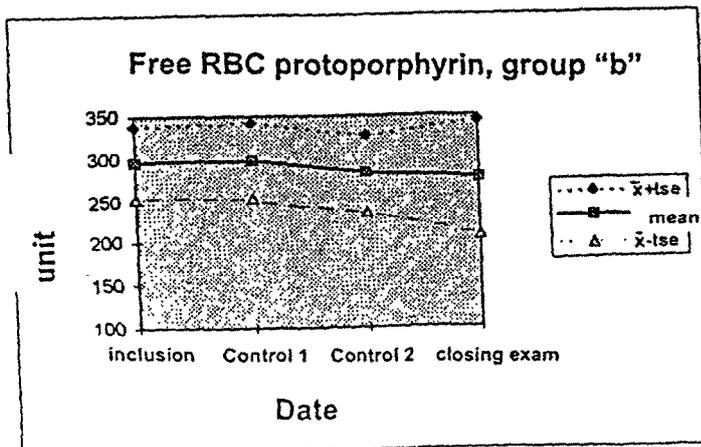
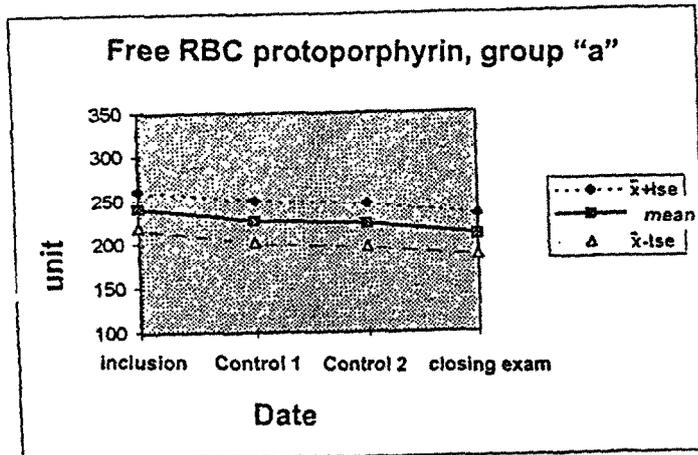
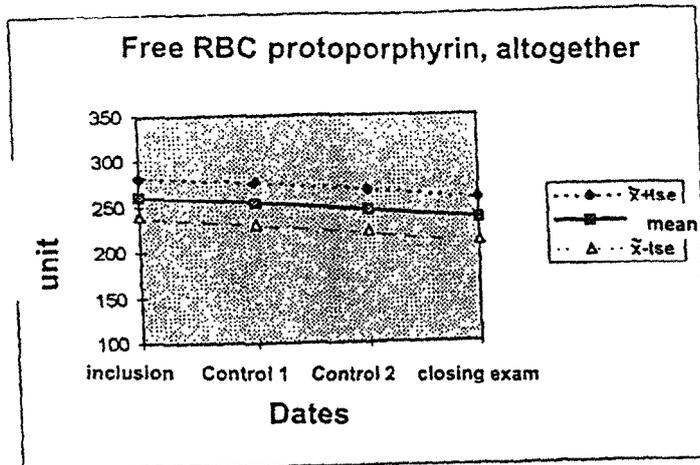


Figure 3. Development of Se Fe level during the trial (_mol)

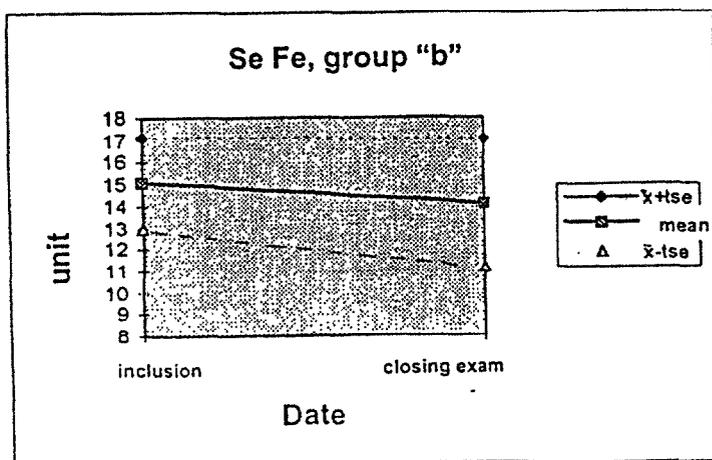
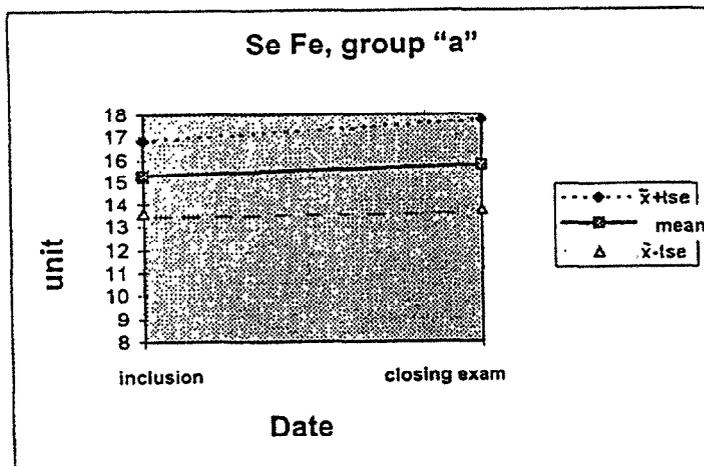
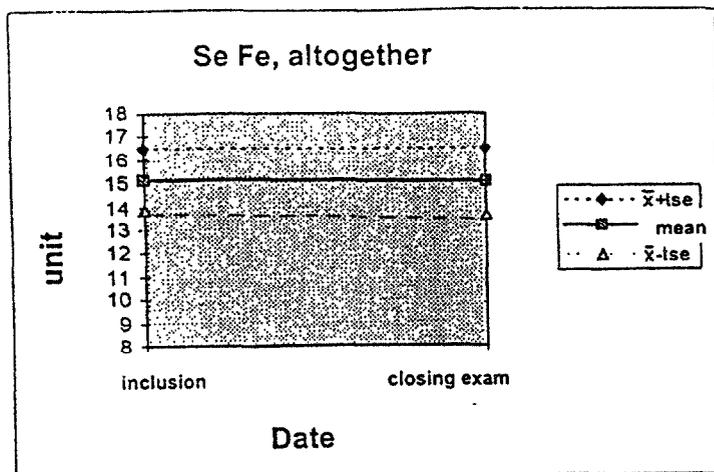


Figure 4. Development of Se transferrin (g/l)

