



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NOV 13 1990

Cook, Inc.
Attn: April Lavender
925 South Curry Pike
P. O. Box 489
Bloomington, Indiana 47402

Re: K901337B
Hilal Embolization Microcoil™
Dated: October 4, 1990
Received: October, 5, 1990
Regulatory Class: III

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

Dear Ms. Lavender:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent to devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments. You may, therefore, market the device, subject to the general controls provisions of the Federal Food, Drug, and Cosmetic Act (act). The general controls provisions of the act include requirements for annual registration, listing of devices, good manufacturing practices, and labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Performance Standards) or class III (Premarket Approval) it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. In addition, the Food and Drug Administration (FDA) may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under the Radiation Control for Health and Safety Act of 1968, or other Federal laws or regulations.

This letter immediately will allow you to begin marketing your device as described. An FDA finding of substantial equivalence of your device to a pre-Amendments device results in a classification for your device and permits your device to proceed to the market, but it does not mean that FDA approves your device. Therefore, you may not promote or in any way represent your device or its labeling as being approved by FDA. If you desire specific advice on the labeling for your device, please contact the Division of Compliance Operations, Regulatory Guidance Branch (HFZ-323) at (301) 427-1116. Other general information on your responsibilities under the act, may be obtained from the Division of Small Manufacturers Assistance at their toll free number (800) 638-2041 or at (301) 443-6597.

Sincerely yours,

George C. Murray, Ph.D.
Director
Division of Anesthesiology, Neurology,
and Radiology Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

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Memorandum

Dr

From

Subject

To

11/8/90
 REVIEWER(S) - NAME(S) A Doyle Gantt Biomedical Engineer
 510(k) NOTIFICATION K901337/B HF-7430

It is my recommendation that the subject 510(k) Notification:

- (A) Is substantially equivalent to marketed devices.
- (B) Requires premarket approval. NOT substantially equivalent to marketed devices.
- (C) Requires more data.
- (D) Other (e.g., exempt by regulation, not a device, duplicate, etc.)

Additional Comments:

Evidence established on the basis of clinical data.

The submitter requests under 21 CFR §807.95:

- No Confidentiality
- Confidentiality for 90 days
- Continued Confidentiality exceeding 90 days

Predicate Product Code w/Panel and class:

84 HCG *presently*
class III

Additional Product Code(s) w/Panel (optional):

REVIEW:

(BRANCH CHIEF)

[Signature] 4/9/90

(DATE)

FINAL REVIEW:

(DIVISION DIRECTOR)

[Signature]

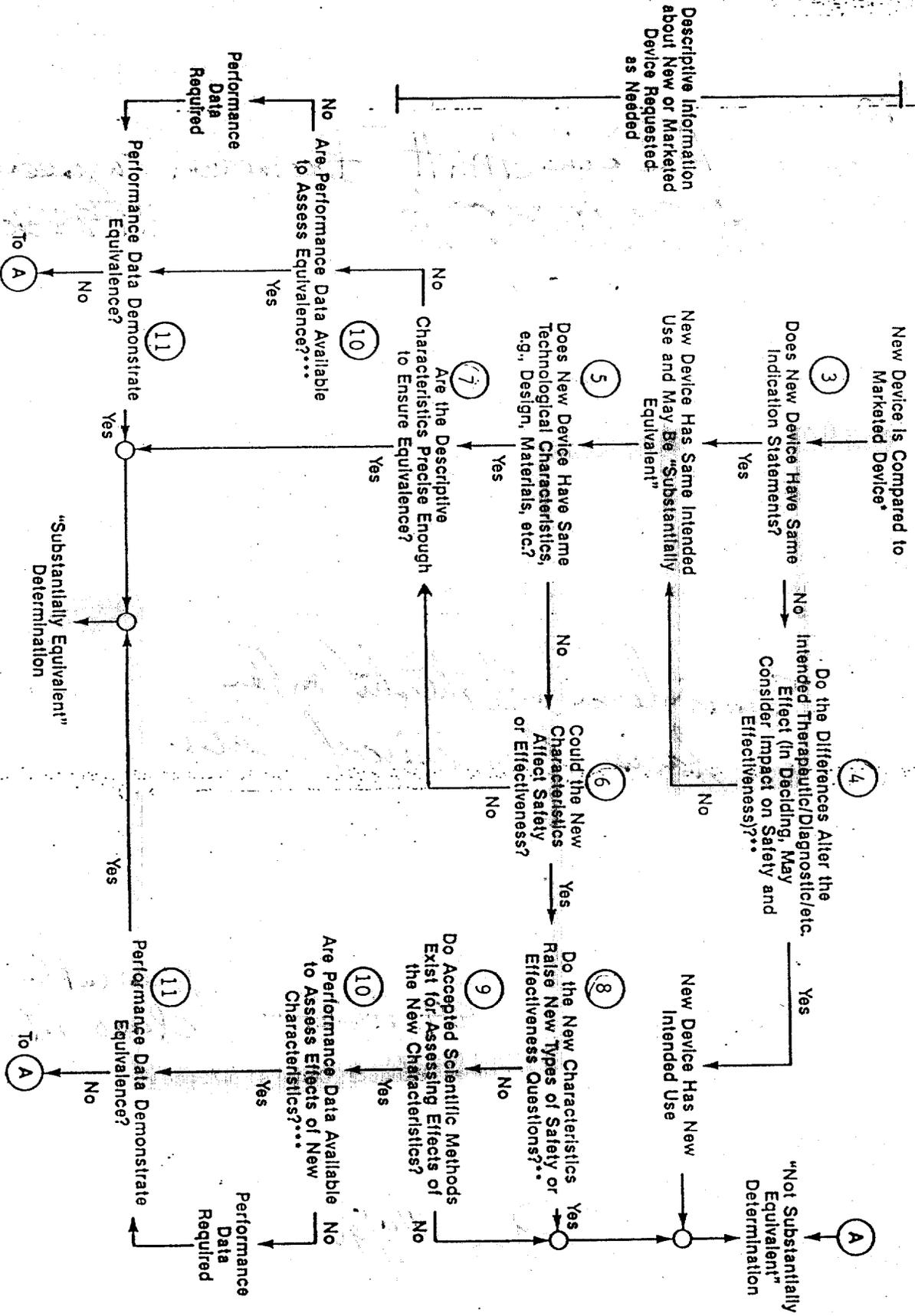
4/13/90

(DATE)

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X
2

510(k) "Substantial Equivalence" Decision-Making Process (Detailed)



* 510(k) Submissions Compare New Devices to Marketed Devices. FDA Requests Additional Information If the Relationship Between Marketed and "Predicted"

** This Decision is Normally Based on Descriptive Information Alone, But Limited Testing Information is Sometimes Required. *** Note that in the 510(k) Other 510(k) The Center's Classification Files or the Literature

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510(K) REVIEW

K901337B

COMPANY NAME: Cook, Inc.

DEVICE NAME: Hilal Embolization Microcoil (TM)

- 1. Is this device life-supporting or life-sustaining?: yes
- 2. Is this an implanted device (short-term or long-term)?: yes, short-term
- 3. If device incorporates a microprocessor, does the firm certify that testing has shown all system requirements are fulfilled and that software changes will require retesting before release? Estimated level of concern is: (Major, Moderate, Minor) not applicable

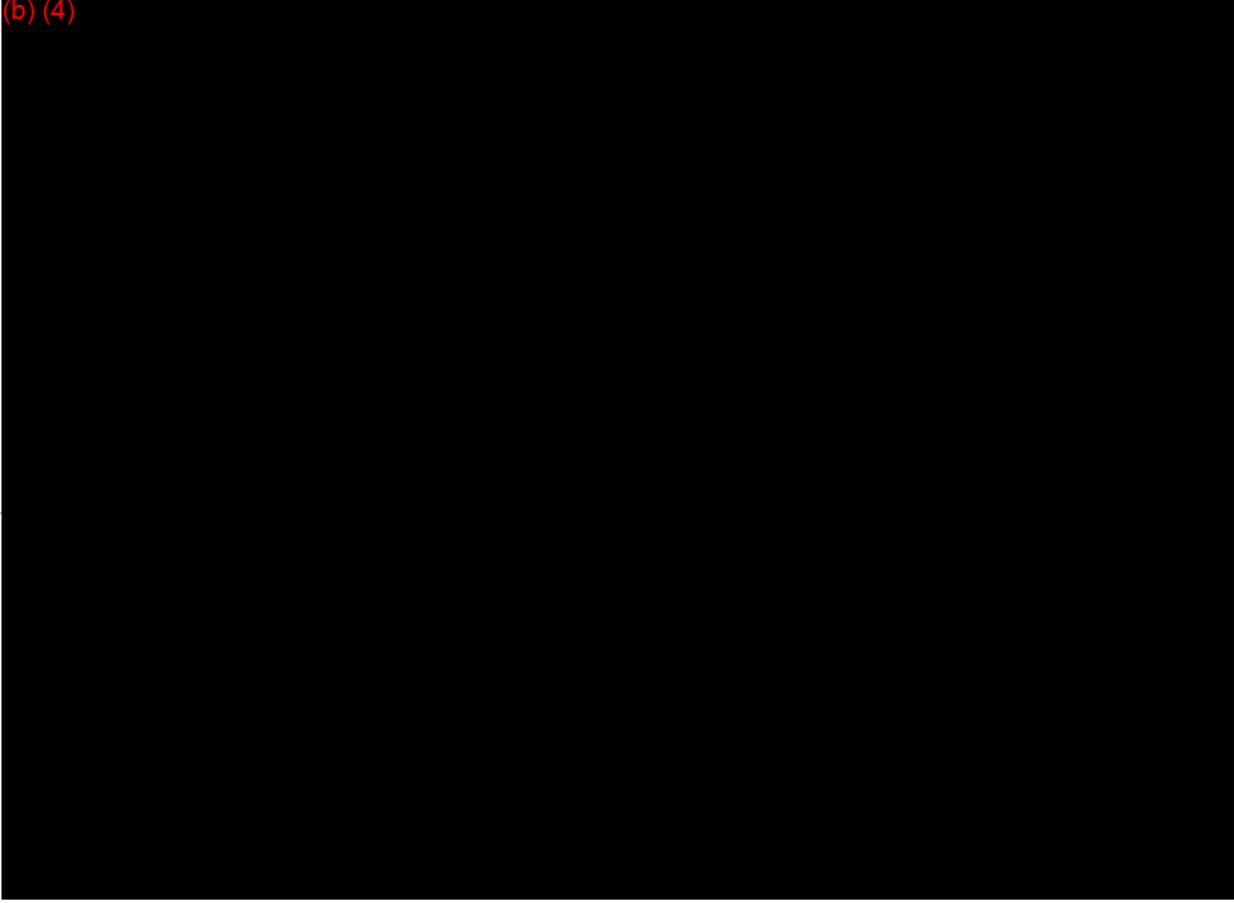
4. Prior device(s) and manufacturer to which this device can be compared:

Cook MWCE (Occluding Spring Embolus) and WCE (Gianturco) embolization coils manufactured by Cook, Inc.

Spiral Platinum Coils manufactured by Target Therapeutics (See K891688B.)

- 5. Submission provides comparative specifications yes
- comparative bench test or in vitro data yes
- summary of animal testing yes
- summary of clinical testing yes
- reference to industry stds. n/a

6. (b) (4)



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(b) (4)

7. RECOMMENDATION:

I believe that this device is equivalent to: 84 HCG

Classification should be based on:

882.5950 Artificial Embolization Device

Present Class: III

DATE: November 8, 1990


A. Doyle Gantt

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5

K 90133TB "SUBSTANTIAL EQUIVALENCE" (SE) DECISION MAKING DOCUMENTATION

REVIEWER: Doyle Gant DIVISION/BRANCH: DANRD/NOB

TRADE NAME: Hilal Embolization Microcoil COMMON NAME: Artificial Embolization Device

PRODUCT TO WHICH COMPARED: see attached review
(510(k) NUMBER IF KNOWN)

- | | | | | |
|-----|---|-------------------------------------|-------------------------------------|--|
| | | YES | (NO) | |
| 1. | IS PRODUCT A DEVICE? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | - IF NO STOP |
| 2. | DEVICE SUBJECT TO 510(k)? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | - IF NO STOP |
| 3. | SAME INDICATION STATEMENT? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | - IF YES GO TO 5 |
| 4. | DO DIFFERENCES ALTER THE EFFECT OR RAISE NEW ISSUES OF SAFETY OR EFFECTIVENESS? | <input type="checkbox"/> | <input type="checkbox"/> | - IF YES STOP - NE  |
| 5. | SAME TECHNOLOGICAL CHARACTERISTICS? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | - IF YES GO TO 7 |
| 6. | COULD THE NEW CHARACTERISTICS AFFECT SAFETY OR EFFECTIVENESS? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | - IF YES GO TO 8 |
| 7. | DESCRIPTIVE CHARACTERISTICS PRECISE ENOUGH? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | - IF NO GO TO 10
- IF YES STOP - SE  |
| 8. | NEW TYPES OF SAFETY OR EFFECTIVENESS QUESTIONS? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | - IF YES STOP - NE  |
| 9. | ACCEPTED SCIENTIFIC METHODS EXIST? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | - IF NO STOP - NE  |
| 10. | PERFORMANCE DATA AVAILABLE? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | - IF NO REQUEST DAT. |
| 11. | DATA DEMONSTRATE EQUIVALENCE? | <input checked="" type="checkbox"/> | <input type="checkbox"/> |  |

NOTE: IN ADDITION TO COMPLETING PAGE TWO, "YES" RESPONSES TO QUESTIONS 4, 6, 8, AND 11, AND EVERY "NO" RESPONSE REQUIRES AN EXPLANATION ON PAGE THREE AND/OR FOUR

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EXPLANATIONS TO "YES" AND "NO" ANSWERS TO QUESTIONS ON PAGE 1 AS NEEDED

1. EXPLAIN WHY NOT A DEVICE: _____

2. EXPLAIN WHY NOT SUBJECT TO 510(k): _____

3. HOW DOES THE NEW INDICATION DIFFER FROM THE PREDICATE DEVICE'S INDICATION: _____

4. EXPLAIN WHY THERE IS OR IS NOT A NEW EFFECT OR SAFETY OR EFFECTIVENESS ISSUE: _____

5. DESCRIBE THE NEW TECHNOLOGICAL CHARACTERISTICS: _____

6. EXPLAIN HOW NEW CHARACTERISTICS COULD OR COULD NOT AFFECT SAFETY OR EFFECTIVENESS: _____

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8

7. EXPLAIN HOW DESCRIPTIVE CHARACTERISTICS ARE NOT PRECISE ENOUGH: _____

8. EXPLAIN NEW TYPES OF SAFETY OR EFFECTIVENESS QUESTIONS RAISED OR WHY THE QUESTIONS ARE NOT NEW: _____

9. EXPLAIN WHY EXISTING SCIENTIFIC METHODS CAN NOT BE USED: _____

10. EXPLAIN WHAT PERFORMANCE DATA IS NEEDED: _____

11. EXPLAIN HOW THE PERFORMANCE DATA DEMONSTRATES THAT THE DEVICE IS OR IS NOT SUBSTANTIALLY EQUIVALENT: _____

ATTACH ADDITIONAL SUPPORTING INFORMATION

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
1390 Piccard Drive
Rockville, Maryland 20850

OCTOBER 10, 1990

COOK, INC.
ATTN: APRIL LAVENDER
925 SOUTH CURRY PIKE
P.O. BOX 489
BLOOMINGTON, IN 47402

D.C. Number : K901337
Received : 10-05-90
90th Day : 01-03-91
Product : HILAL EMBOLIZATION
MICROCOIL(TM)

The additional information you have submitted has been received.

- We will notify you when the processing of this submission has been completed or if any additional information is required. You are required to wait ninety (90) days after the received date shown above or until receipt of a "substantially equivalent" letter before placing the product into commercial distribution. We intend to complete our review expeditiously and within ninety days. Occasionally, however, a submitter will not receive a final decision or a request for additional information until after ninety days has elapsed. Be aware that FDA is able to continue the review of a submission beyond the ninety day period and might conclude that the device is not substantially equivalent. A "not substantially equivalent" device may not be in commercial distribution without an approved premarket approval application or reclassification of the device. We, therefore, recommend that you not market this device before FDA has made a final decision. Thus, if you have not received a decision within ninety days, it would be prudent to check with FDA to determine the status of your submission.

All correspondence concerning your submission MUST be sent to the Document Mail Center at the above address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification application. Telefax material will not be accepted nor considered as part of your official premarket notification application, unless specifically requested of you by an FDA official.

If you have procedural or policy questions, please contact the Division of Small Manufacturers Assistance at (301) 443-6597 or their toll-free number (800) 638-2041, or contact me at (301) 427-1190.

Sincerely yours,

Robert I. Chissler
Premarket Notification Coordinator
Office of Device Evaluation
Center for Devices and
Radiological Health

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MEDICAL ENGINEERING AND
DEVELOPMENT INSTITUTE, INCORPORATED
A COOK GROUP COMPANY
P.O. Box 2402 West Lafayette, IN 47906
Phone: 317 463-7537
Telefax: 317 497-0641

K901337/B

MED

INSTITUTE

October 4, 1990

Mr. Doyle Gant
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
1390 Piccard Drive
Rockville, MD 20850

FDA/ODRM/ODE/DHG

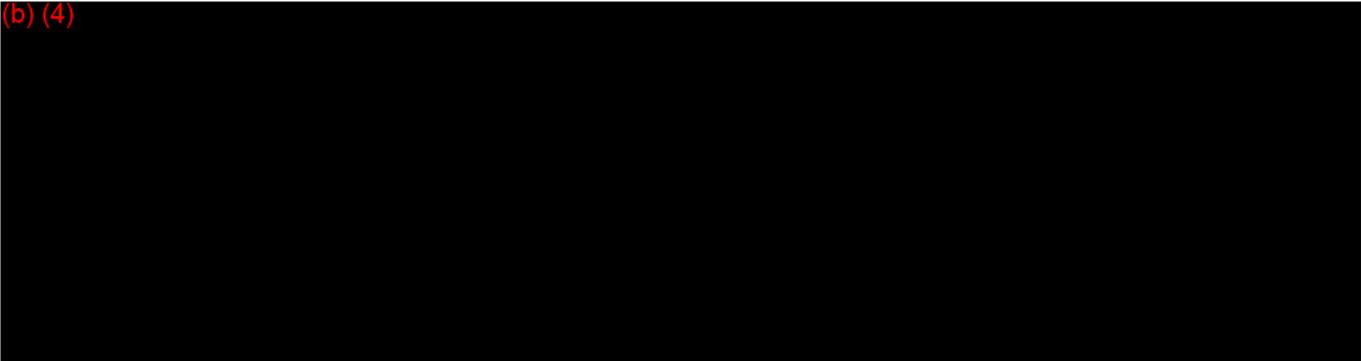
5 OCT 1990 13 20

RECEIVED

Dear Mr. Gant:

Enclosed is the additional information you requested regarding the 510(k) submission of the Hilal Microcoil™ D.C. #K885124/K901337.

(b) (4)



We consider our intent to market this device as confidential commercial information and request that it be considered as such by the FDA and not available through Freedom of Information except where required by law. We have not disclosed our intent to market this device to anyone except employees of our establishment and have taken precautions to protect this confidentiality.

We believe the additional information enclosed will allow you to complete your review of substantial equivalency of the Hilal Microcoil™. If further clarification is necessary, please address technical concerns to Neal Fearnot, Ph.D. (317) 463-7537 and administrative concerns to April Lavender (812) 339-2235.

Sincerely,

Neal E. Fearnot (enc)

Neal E. Fearnot, Ph.D., E.E.

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11

MEDICAL ENGINEERING AND
DEVELOPMENT INSTITUTE, INCORPORATED
A COOK GROUP COMPANY
P.O. Box 2402 West Lafayette, IN 47906
Phone: 317 463-7537
Telefax: 317 497-0641

MED

INSTITUTE

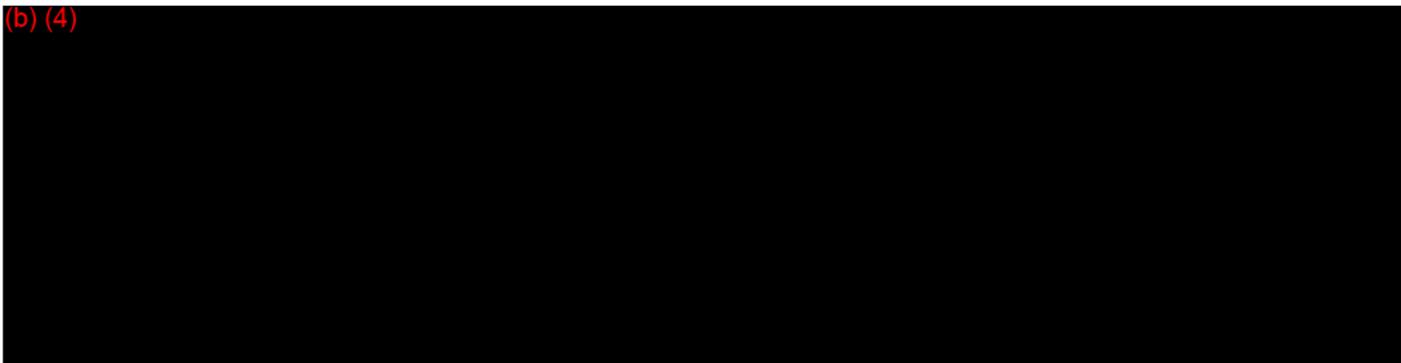
October 4, 1990

Mr. Doyle Gant
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
1390 Piccard Drive
Rockville, MD 20850

RECEIVED
5 Oct 90 13 20
FDA/CDRH/ODE/DNC

Dear Mr. Gant:

Enclosed is the additional information you requested regarding the 510(k) submission of the Hilal Microcoil™ D.C. #K885124/K901337.



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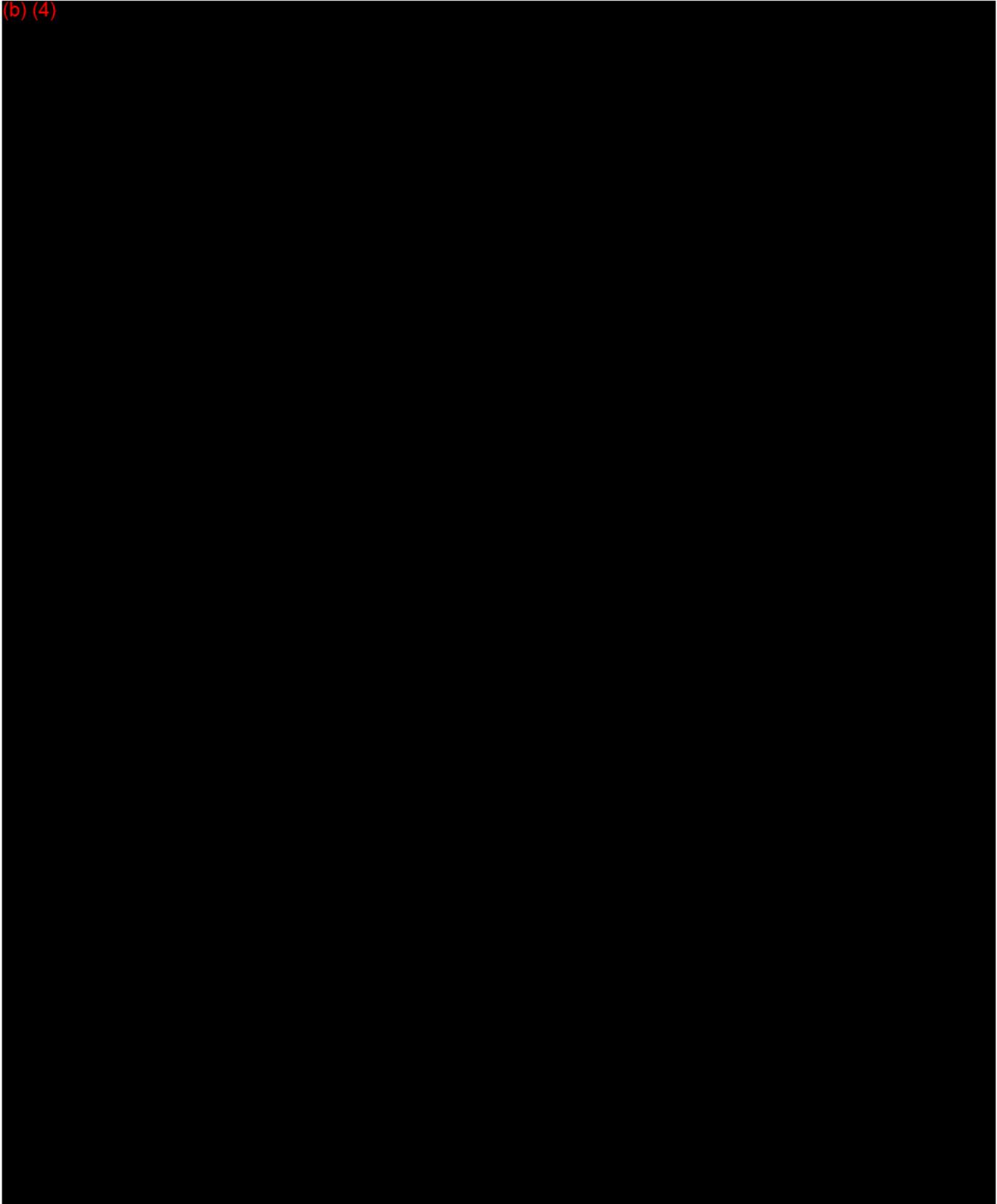
Sincerely,

Neal E. Fearnot, Ph.D., E.E.

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12

(b) (4)



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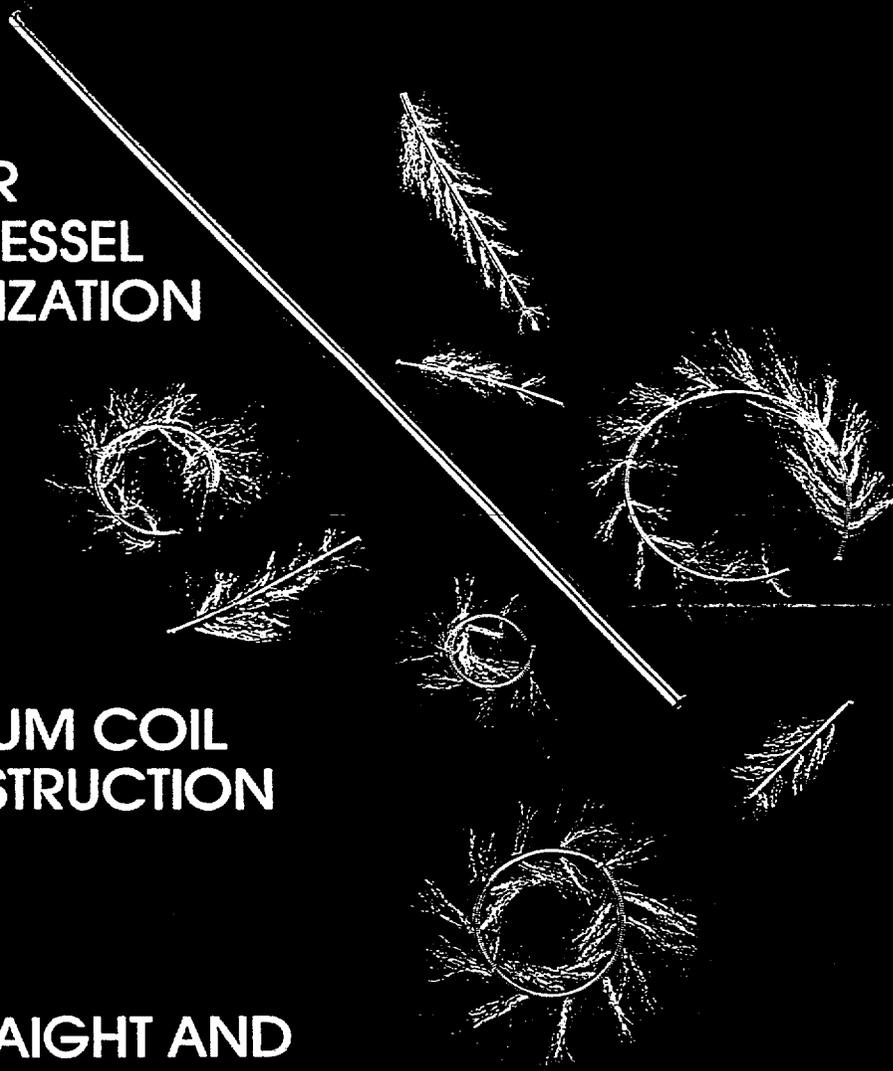
13

HILAL EMBOLIZATION MICROCOILS™

- IDEAL FOR
SMALL VESSEL
EMBOLIZATION

- PLATINUM COIL
CONSTRUCTION

- STRAIGHT AND
CURLED DESIGNS



HILAL EMBOLIZATION MICROCOILS™

STRAIGHT

Used for arterial embolization of selective vessel supply to arterio-venous malformations and other vascular lesions of the brain, spinal cord and spine when surgical resection is anticipated or desired. Design of the Microcoils™ permits introduction through small, pre-positioned delivery catheters. Unique, straight, non-curling design permits delivery into the target vessel by saline flush after initial advancement through the straightest segment of the catheter using the wire guide. The coils are made of platinum, easily detected radiographically, with spaced synthetic fibers to promote maximum thrombogenicity. Final positioning of Microcoils™ creates a "platinum cast" effect within the vessel lumen. Supplied sterile in peel-open packages. Intended for one-time use.



MICROCOIL™
Platinum with synthetic fibers

ORDER NUMBER	Length ¹	Configuration	Remarks
MWCE-18-0.5-0-HILAL	.5 cm	Straight	
MWCE-18-0.7-0-HILAL	.7 cm	Straight	
MWCE-18-1.0-0-HILAL	1.0 cm	Straight	Supplied 2 each per package
MWCE-18-1.5-0-HILAL	1.5 cm	Straight	

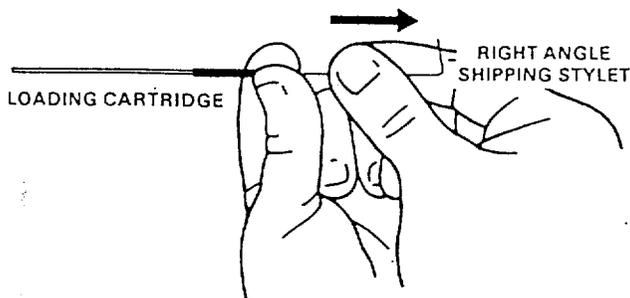
¹Other coil lengths available upon request

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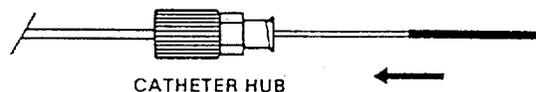
DELIVERY CATHETER AND WIRE GUIDE RECOMMENDATIONS FOR STRAIGHT AND CURLED MICROCOILS™

- Microcoils™ are recommended for use through catheters designed for use with .018 inch (0.46 mm) diameter wire guides and whose inner diameter (ID) does not exceed .027 inch (0.69 mm) diameter. NOTE: Cook catheters appropriate for use are non-tapered T3.0 and T3.0S Teflon[®] catheters.
- Microcoils™ are not recommended for use with polyurethane or polyvinylchloride catheters.
- Wire guides recommended for loading and positioning Microcoils™ are Teflon[®] coated .018 inch (0.46 mm) diameter with flexible tapered tips. NOTE: Cook Order Numbers: TSFNA-18-180, TSFNB-18-180.

TO LOAD MICROCOIL™ INTO DELIVERY CATHETER



1. Firmly grasp Microcoil™ loading cartridge between thumb and forefinger at point where right angle shipping styllet exits.
2. While maintaining firm finger grip, remove shipping styllet. This will prevent Microcoil™ from exiting cartridge. Verify its position inside cartridge by direct vision.



3. Position loading cartridge into base of hub of catheter.



4. Using .018 inch (0.46 mm) diameter wire guide, push Microcoil™ out of loading cartridge and into catheter lumen.
5. Remove loading cartridge.

15

HILAL EMBOLIZATION MICROCOILS™

CURLED

Used for arterial and venous embolizations and other vascular lesions of the brain, spinal cord and spine when surgical resection is anticipated or desired. Design of the Microcoils™ permits introduction through small pre-positioned delivery catheters. Deployment of coils into the vessel lumen is accomplished utilizing standard wire guide pusher techniques. The coils are made of platinum, easily detected radiographically, with spaced synthetic fibers to promote maximum thrombogenicity. Supplied sterile in peel-open packages. Intended for one-time use.



MICROCOIL™
Platinum with synthetic fibers

ORDER NUMBER	Curled Diameter	Length	Configuration	Remarks
MWCE-18-1.0-3-HILAL	3 mm	1.0 cm	Curled	
MWCE-18-1.5-5-HILAL	5 mm	1.5 cm	Curled	
MWCE-18-2.1-7-HILAL	7 mm	2.1 cm	Curled	Supplied 2 each per package
MWCE-18-3.0-10-HILAL	10 mm	3.0 cm	Curled	

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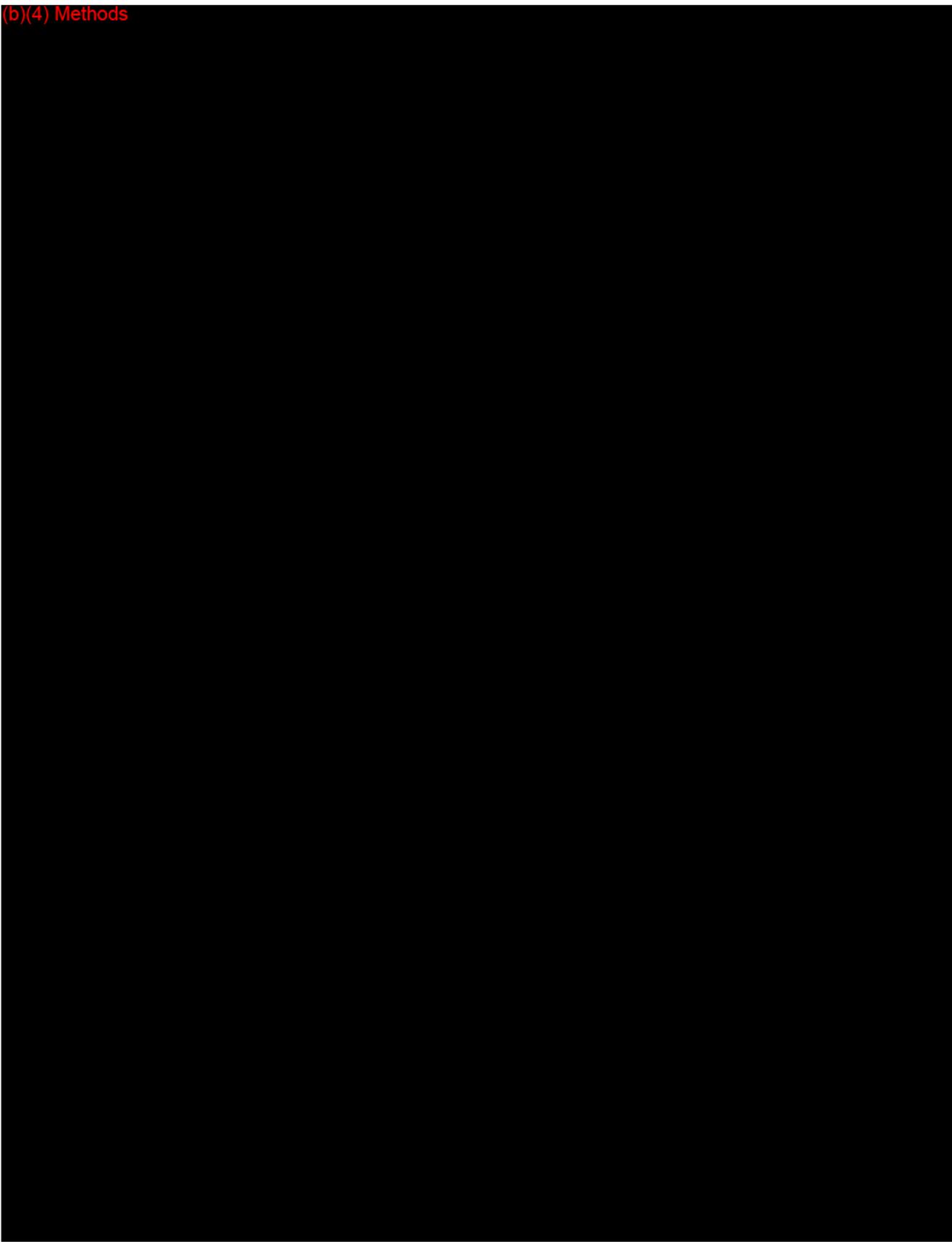
REFERENCES

S. Hilal, M.D., Department of Radiology, The Neurological Institute, New York, New York.

S. Hilal, et al: "Synthetic Fiber Coated Platinum Coils Successfully Used for the Endovascular Treatment of Arterio-Venous Malformations, Aneurysms, and Direct Arterio-Venous Fistulae of the Central Nervous System," Scientific paper presented at the 26th Annual Meeting of the American Society of Neuroradiology, Chicago, Illinois, May, 1988.

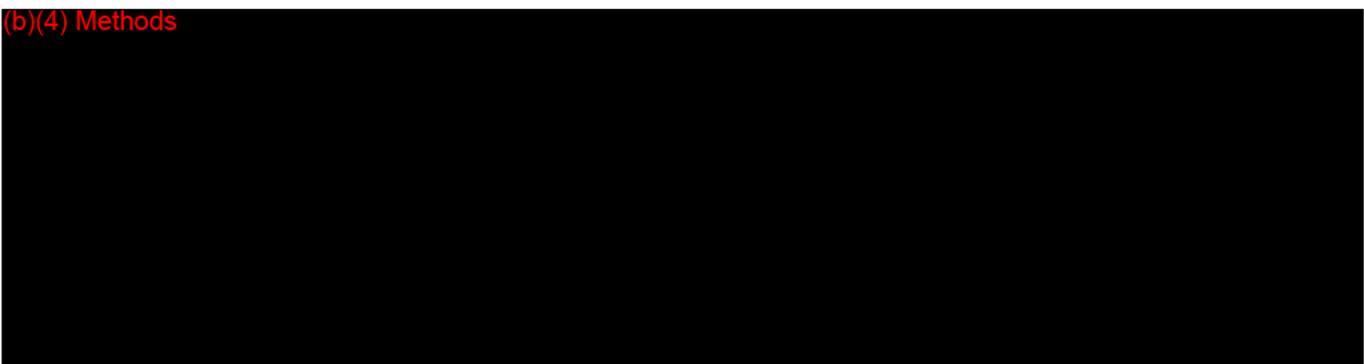
V. P. Chuang, S. Wallace, C. Gianturco: "A New Improved Coil for Tapered Tip Catheter for Arterial Occlusion," *Radiology*, 135 (1980), 507-509.

(b)(4) Methods



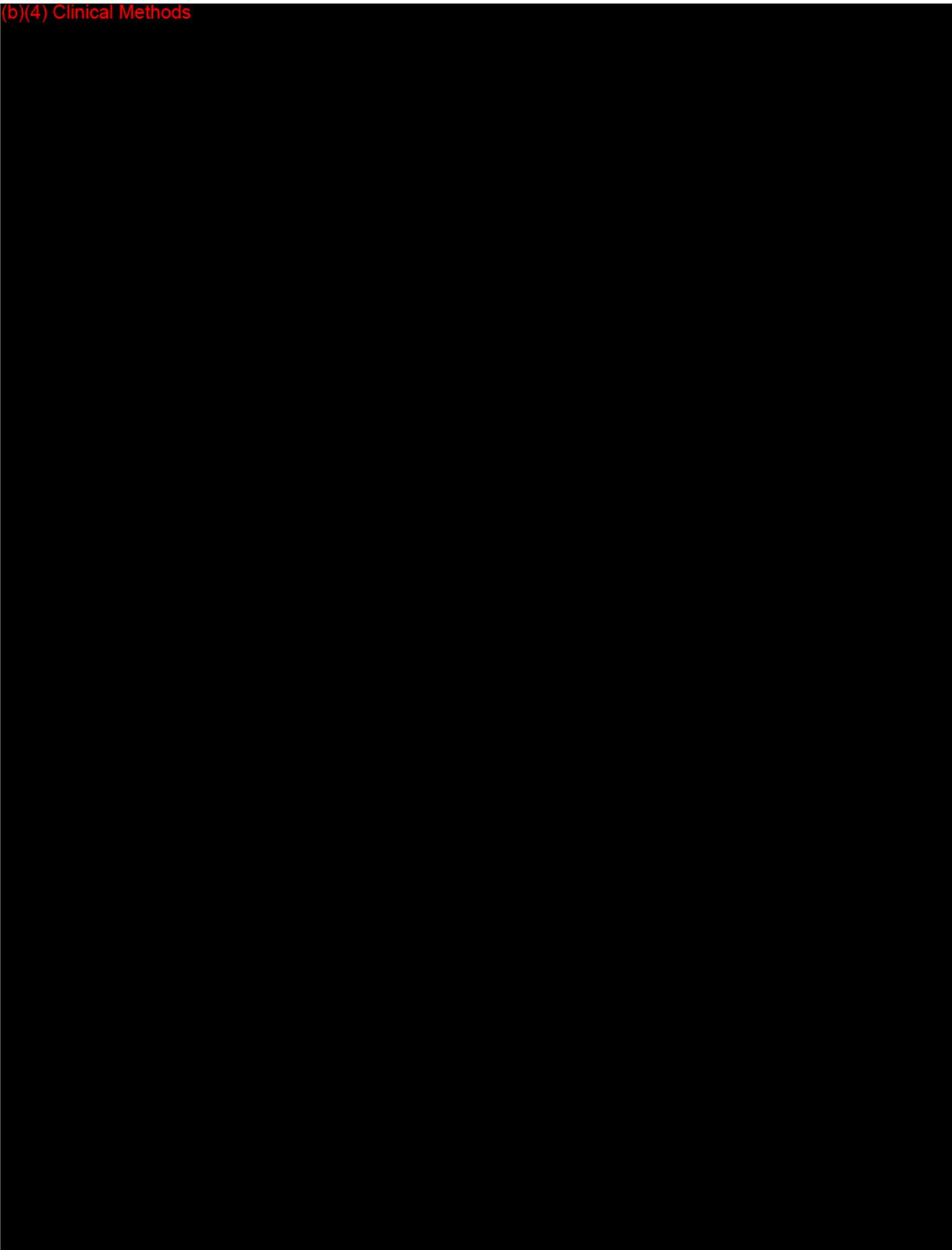
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(b)(4) Methods



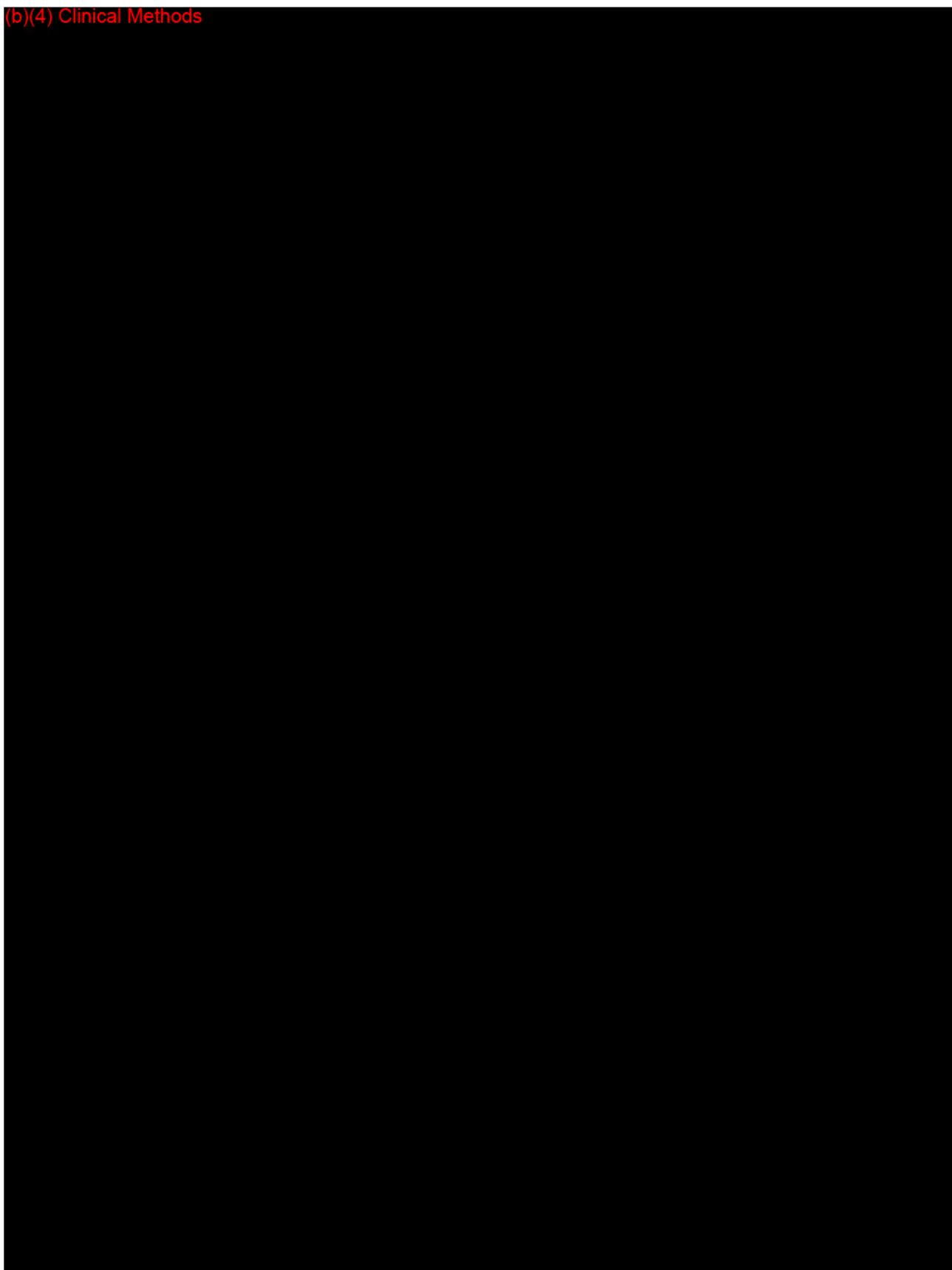
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(b)(4) Clinical Methods



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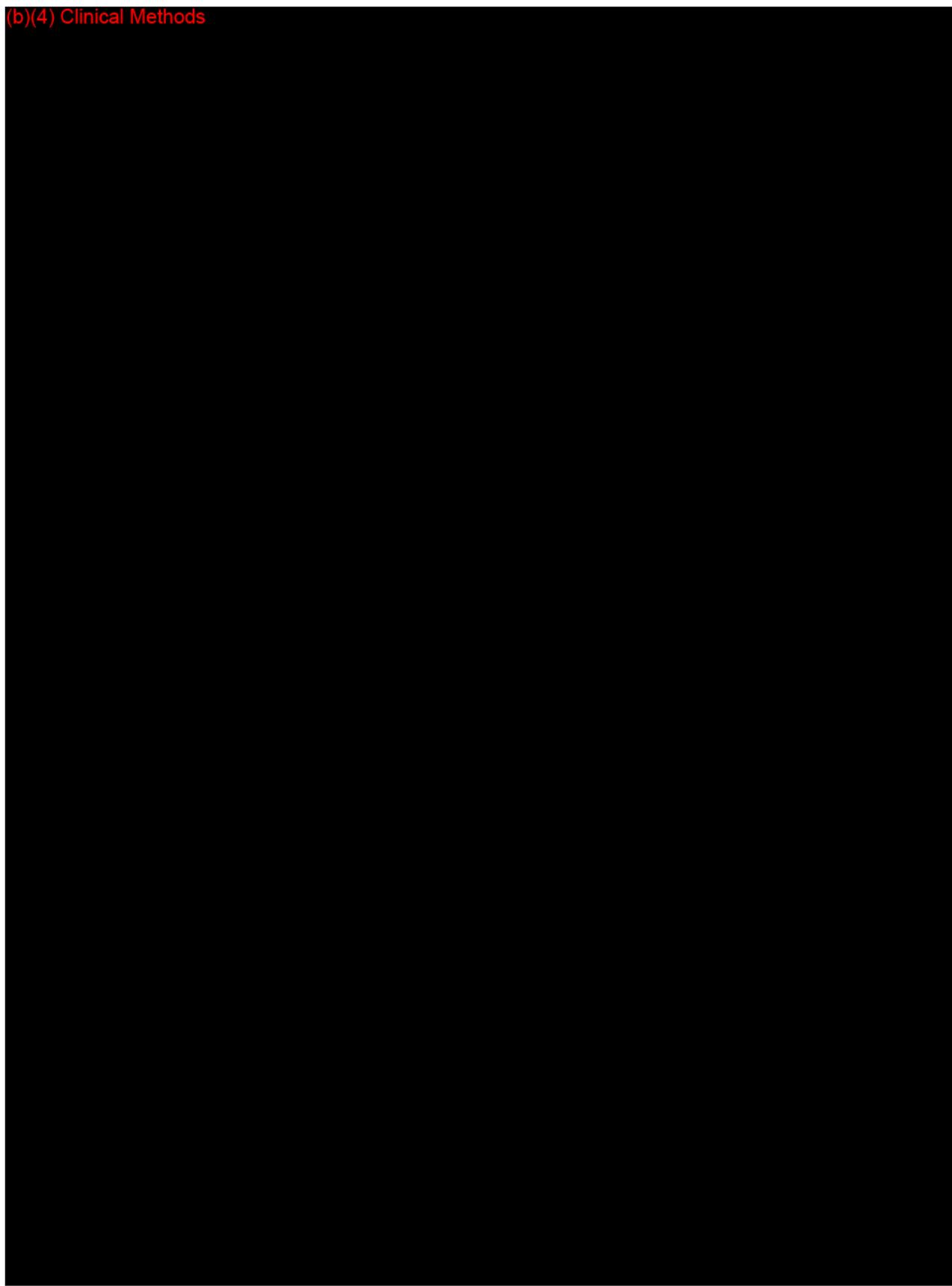
(b)(4) Clinical Methods



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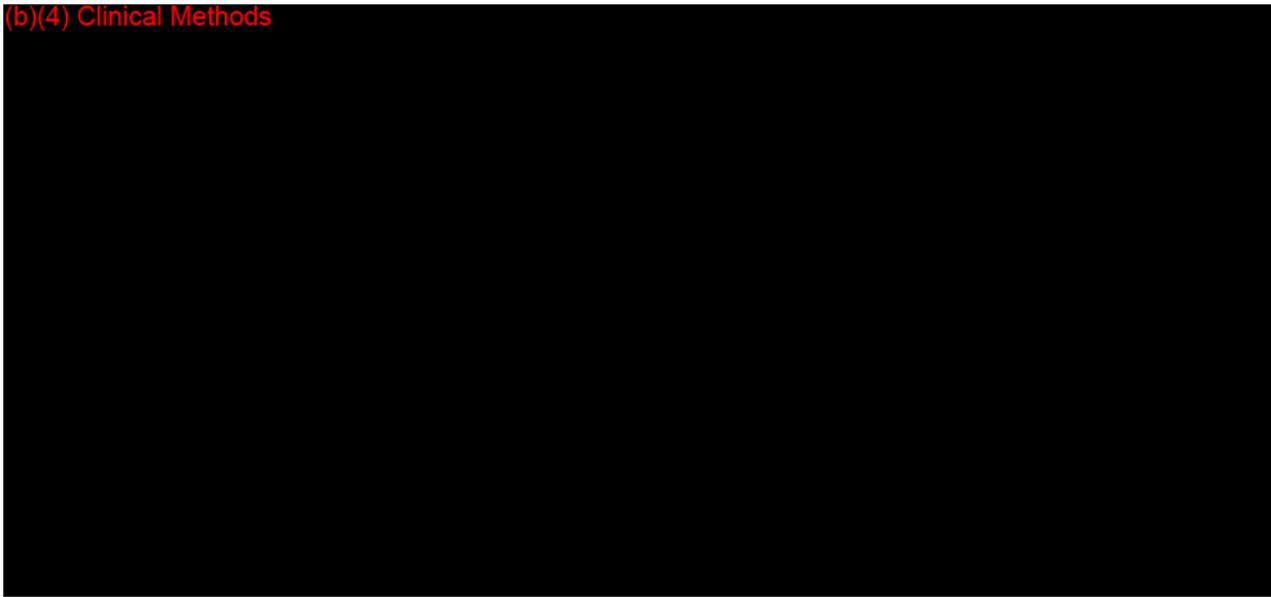
(b)(4) Clinical Methods



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21

(b)(4) Clinical Methods



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JJ

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
1390 Piccard Drive
Rockville, Maryland 20850

AUGUST 31, 1990

COOK, INC.
ATTN: APRIL LAVENDER
925 SOUTH CURRY PIKE
P.O. BOX 489
BLOOMINGTON, IN 47402

D.C. Number: K901337
Product : HILAL EMBOLIZATION
MICROCOIL(TM)

-- We are holding your above-referenced Premarket Notification (510(k)) for 30 days pending receipt of the additional information that was requested by the Office of Device Evaluation. This information and all correspondence concerning your submission MUST be sent in duplicate to the Document Mail Center at the above address (21 CFR 807.90). Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification application. Telefax material will not be accepted nor considered as part of your official premarket notification application, unless specifically requested of you by an FDA official.

When your additional information is received by the Office of Device Evaluation Document Mail Center (address above), the 90-day period will begin again.

If after 30 days the requested information is not received, we will stop reviewing your submission and proceed to withdraw your file from our review system. Pursuant to 21 CFR 20.29, a copy of your 510(k) submission will remain in the Office of Device Evaluation. If you then wish to resubmit this 510(k) notification, a new number will be assigned and the 90-day time period will begin again.

If you have procedural or policy questions, please contact the Division of Small Manufacturers Assistance at (301) 443-6597 or their toll-free number (800) 638-2041, or contact me at (301) 427-1190.

Sincerely yours,

Robert I. Chissler
Premarket Notification Coordinator
Office of Device Evaluation
Center for Devices and
Radiological Health

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DO NOT REMOVE THIS ROUTE SLIP!!!!

K-90-1337

8/31/90

FROM: COOK, INC. ATTN: APRIL LAVENDER 925 SOUTH CURRY PIKE P.O. BOX 489 BLOOMINGTON, IN 47402	LETTER DATE 03/19/90	LOGIN DATE 03/22/90	DUE DATE 10/10/90
	TYPE OF DOCUMENT: 510 (k)		CONTROL # K901337
SHORT NAME: COOK		ESTABLISHMENT NO: 1820334	
NO: ODE/DMC	CONT. CONF.: ? STATUS : H REV PANEL : NE PAN/PROD CODE(S): NE/ / /		
SUBJECT: HILAL EMBOLIZATION MICROCOIL(TM)			
DECISION: DECISION DATE: / /	RQST INFO DATE: 04/30/90 DATE: 08/31/90 DATE: / / DATE: / / DATE: / / DATE: / /	INFO DUE DATE: 09/11/90 DATE: 09/30/90 DATE: / / DATE: / / DATE: / / DATE: / /	

SUPPLEMENT: 01

LTR DATE: 900706

LOGIN DATE: 900712

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24



Memorandum

8/30/90

A. D. Gault

K901337A

From REVIEWER(S) - NAME(S)

Subject 510(k) NOTIFICATION

To THE RECORD

It is my recommendation that the subject 510(k) Notification:

(A) Is substantially equivalent to marketed devices.

(B) Requires premarket approval. NOT substantially equivalent to marketed devices.

(C) Requires more data. (*See telephone memo dated 8/30*)

(D) Other (e.g., exempt by regulation, not a device, duplicate, etc.)

Additional Comments:

The submitter requests under 21 CFR §807.95:

No Confidentiality

Confidentiality for 90 days

Continued Confidentiality exceeding 90 days

Predicate Product Code w/Panel and class:

Additional Product Code(s) w/Panel (optional):

REVIEW:

(BRANCH CHIEF)

[Signature] 8/30/90

(DATE)

FINAL REVIEW:

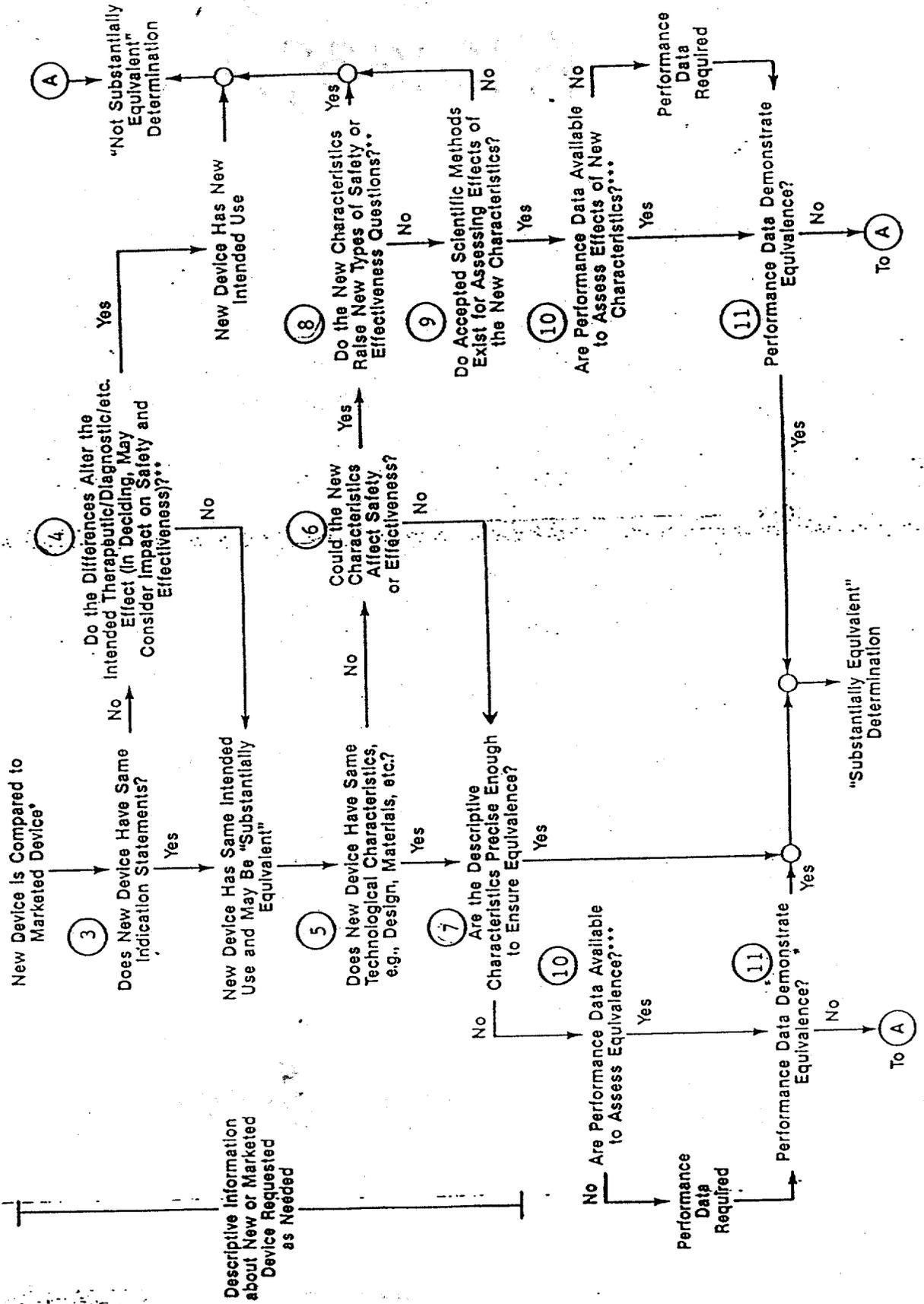
(DIVISION DIRECTOR)

(DATE)

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25

510(k) "Substantial Equivalence" Decision-Making Process (Detailed)



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* 510(k) Substantial Equivalence Determination is Normally Based on Descriptive Information Alone, But Additional Information is Sometimes Required.
 ** The Limiting Information is Sometimes Required.
 *** Note: See 21 CFR 801.109 for the criteria for Substantial Equivalence.

MEMORANDUM OF A TELEPHONE CONVERSATION

Between: A. Doyle Gantt, Biomedical Engineer, Neurological Devices
Branch, Office of Device Evaluation, Food and
Drug Administration, HFZ-430

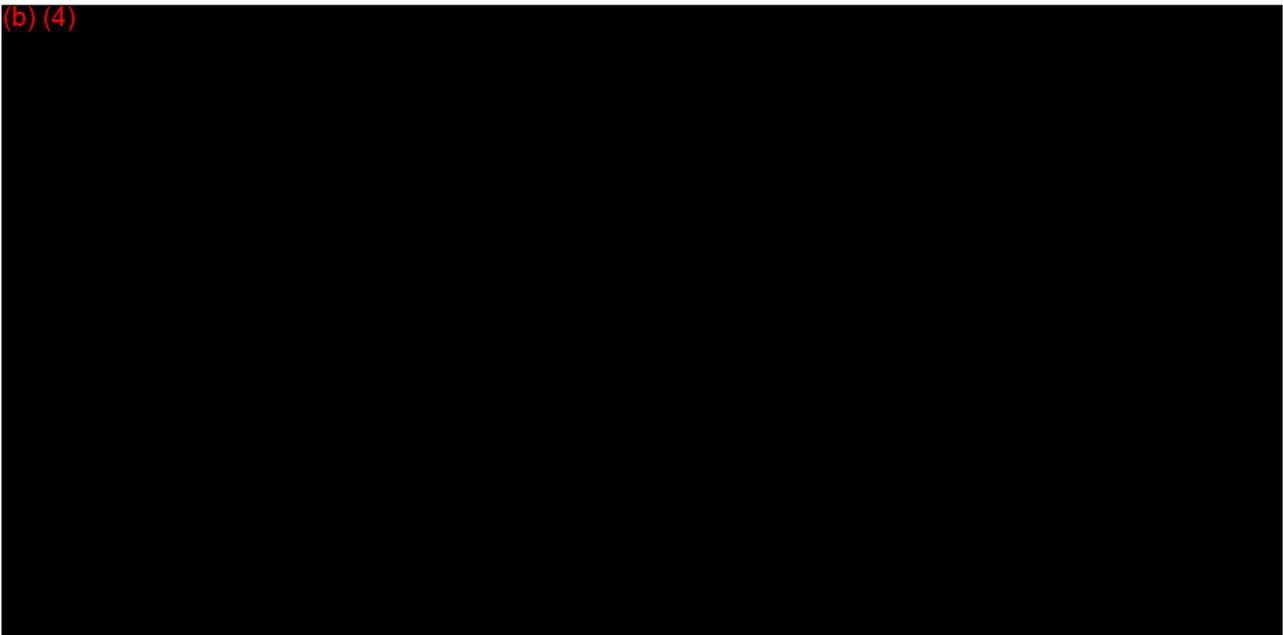
And: [REDACTED] (b) (6)

Date: August 30, 1990

Subject: K901337A - Hilal (tm) Microcoils

Summary: I called (b) (6) today and requested [REDACTED] (b) (4)

(b) (4)



(b) [REDACTED]

A. Doyle Gantt
A. Doyle Gantt

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Review Memorandum

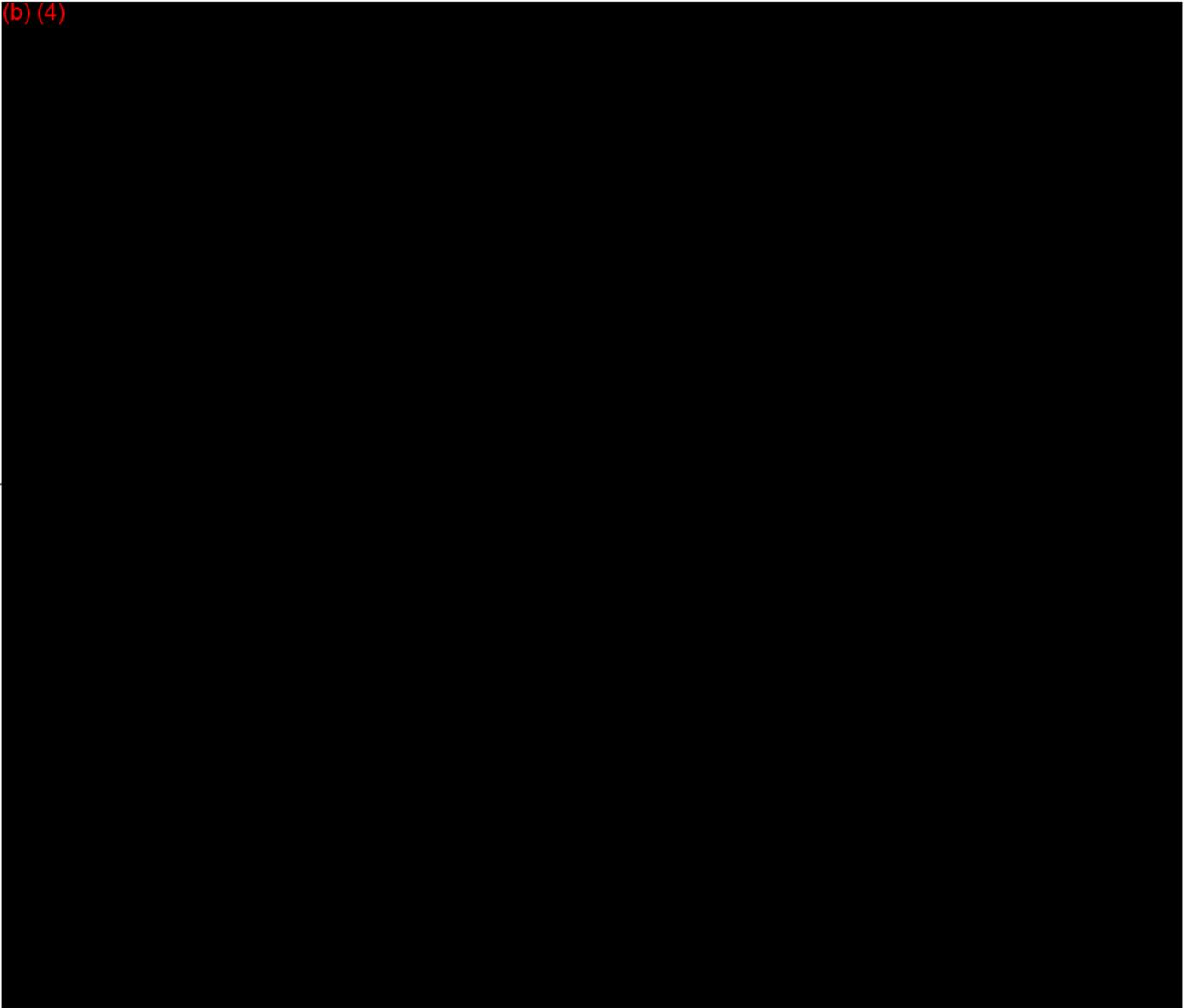
From: John Dawson, Microbiologist, Neurological Devices Branch

To: The File

Date: 8/9/90

Subject: K901337A Hilal Embolization Microcoil

(b) (4)

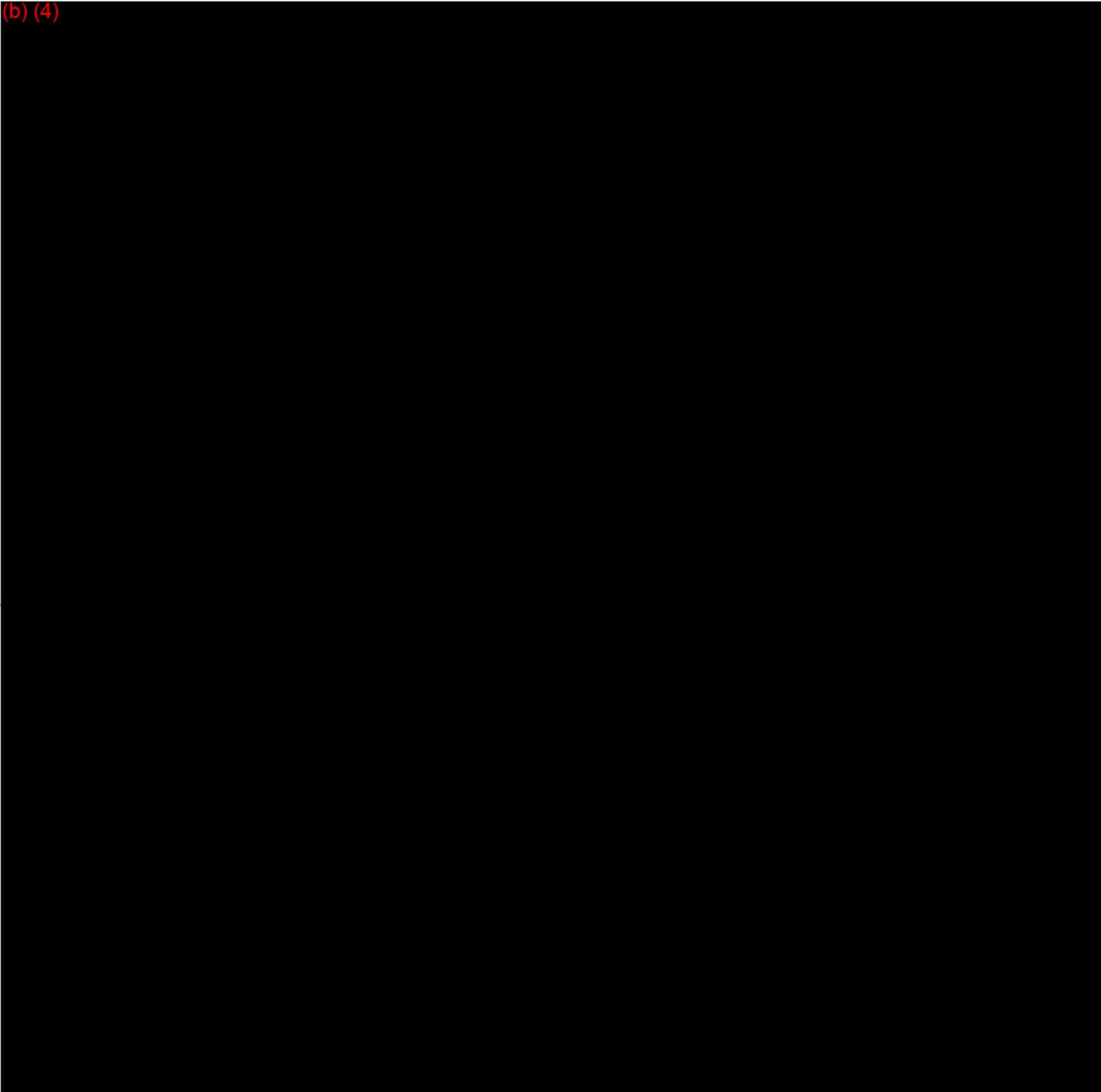


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John Dawson

28

(b) (4)



John Dawson

29

(b) (4)



John Dawson
John Dawson

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Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
1390 Piccard Drive
Rockville, Maryland 20850

JULY 12, 1990

COOK, INC.
ATTN: APRIL LAVENDER
925 SOUTH CURRY PIKE
P.O. BOX 489
BLOOMINGTON, IN 47402

D.C. Number : K901337
Received : 07-12-90
90th Day : 10-10-90
Product : HILAL EMBOLIZATION
MICROCOIL(TM)

The additional information you have submitted has been received.

-- We will notify you when the processing of this submission has been completed or if any additional information is required. You are required to wait ninety (90) days after the received date shown above or until receipt of a "substantially equivalent" letter before placing the product into commercial distribution. We intend to complete our review expeditiously and within ninety days. Occasionally, however, a submitter will not receive a final decision or a request for additional information until after ninety days has elapsed. Be aware that FDA is able to continue the review of a submission beyond the ninety day period and might conclude that the device is not substantially equivalent. A "not substantially equivalent" device may not be in commercial distribution without an approved premarket approval application or reclassification of the device. We, therefore, recommend that you not market this device before FDA has made a final decision. Thus, if you have not received a decision within ninety days, it would be prudent to check with FDA to determine the status of your submission.

All correspondence concerning your submission MUST be sent to the Document Mail Center at the above address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification application. Telefax material will not be accepted nor considered as part of your official premarket notification application, unless specifically requested of you by an FDA official.

If you have procedural or policy questions, please contact the Division of Small Manufacturers Assistance at (301) 443-6597 or their toll-free number (800) 638-2041, or contact me at (301) 427-1190.

Sincerely yours,

Robert I. Chissler
Premarket Notification Coordinator
Office of Device Evaluation
Center for Devices and
Radiological Health

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A COOK GROUP COMPANY
925 South Curry Pike P.O. Box 489
Bloomington, IN 47402 U.S.A.
Phone: 812 339-2235
Telex: 6711161 COOK UW
Telefax: 812 339-5369

K901337/A

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COOK®

Cook Incorporated

FDA/CDRH/ODE/DMC

July 6, 1990

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Mr. Doyle Gant
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
1390 Piccard Drive
Rockville, MD 20850

Dear Mr. Gant:

The following is submitted in response to your request for further information to determine the substantial equivalence of the Hilal Microcoil™ D.C. #K885124/K901337 to pre-Amendment devices with regard to its safety and effectiveness.

(b) (4)



We believe the information enclosed sufficiently addresses your concerns in determining the substantial equivalence of the Hilal Microcoil™. Please address technical questions to Neal Fearnot, Ph.D. (317)463-7537 and administrative questions to April Lavender (812)339-2235.

Sincerely,



- April Lavender

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32

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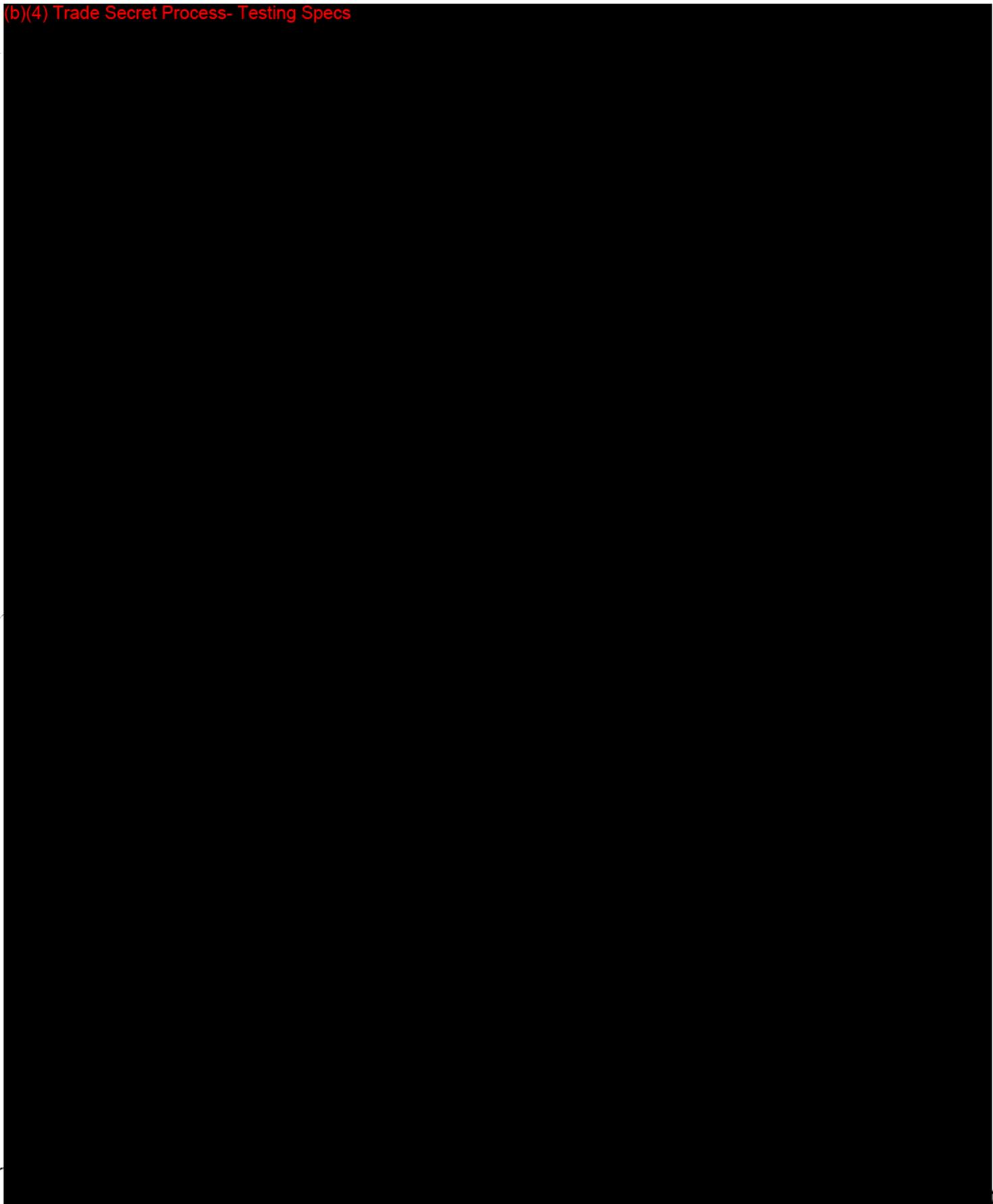
April Lavender

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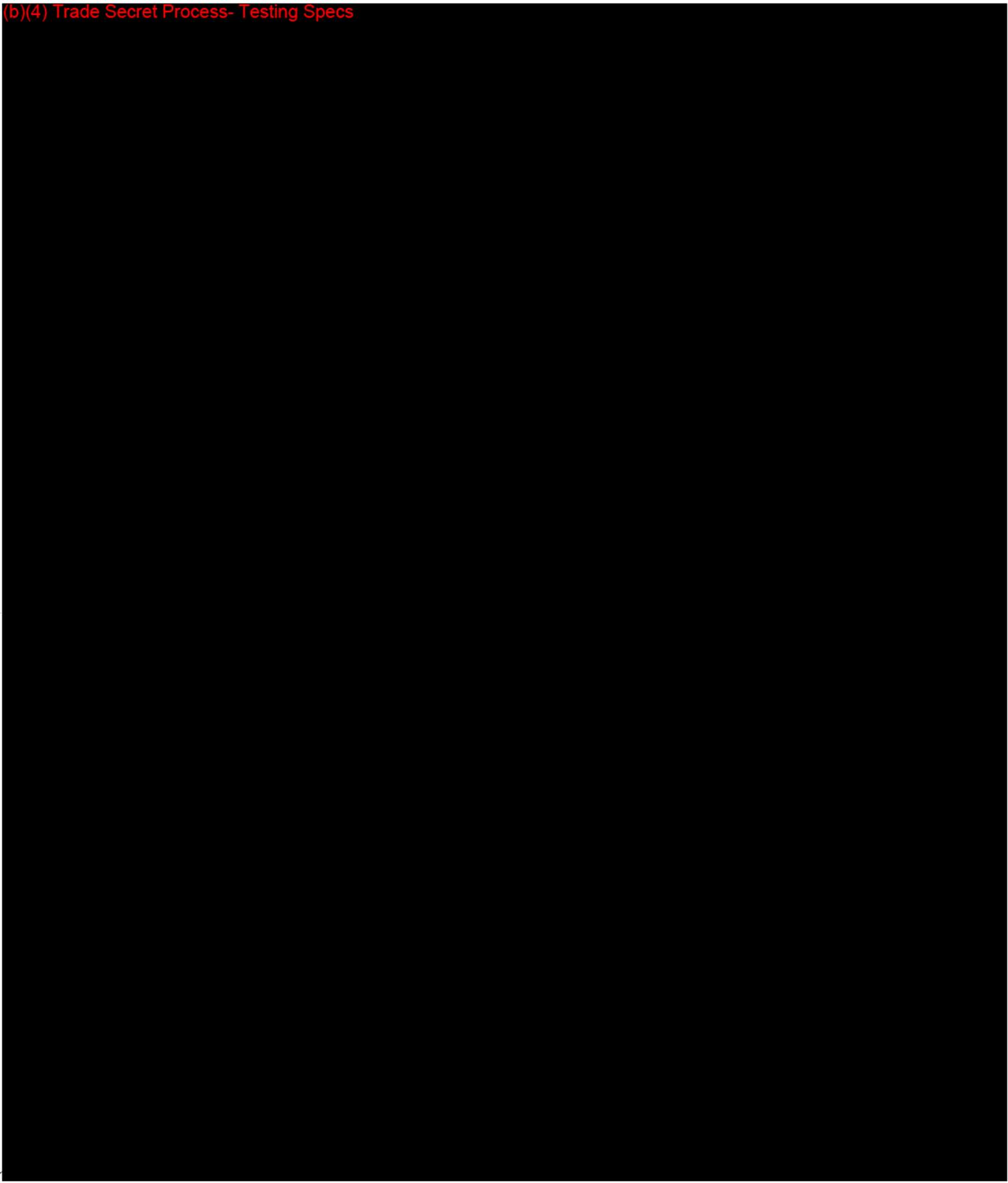
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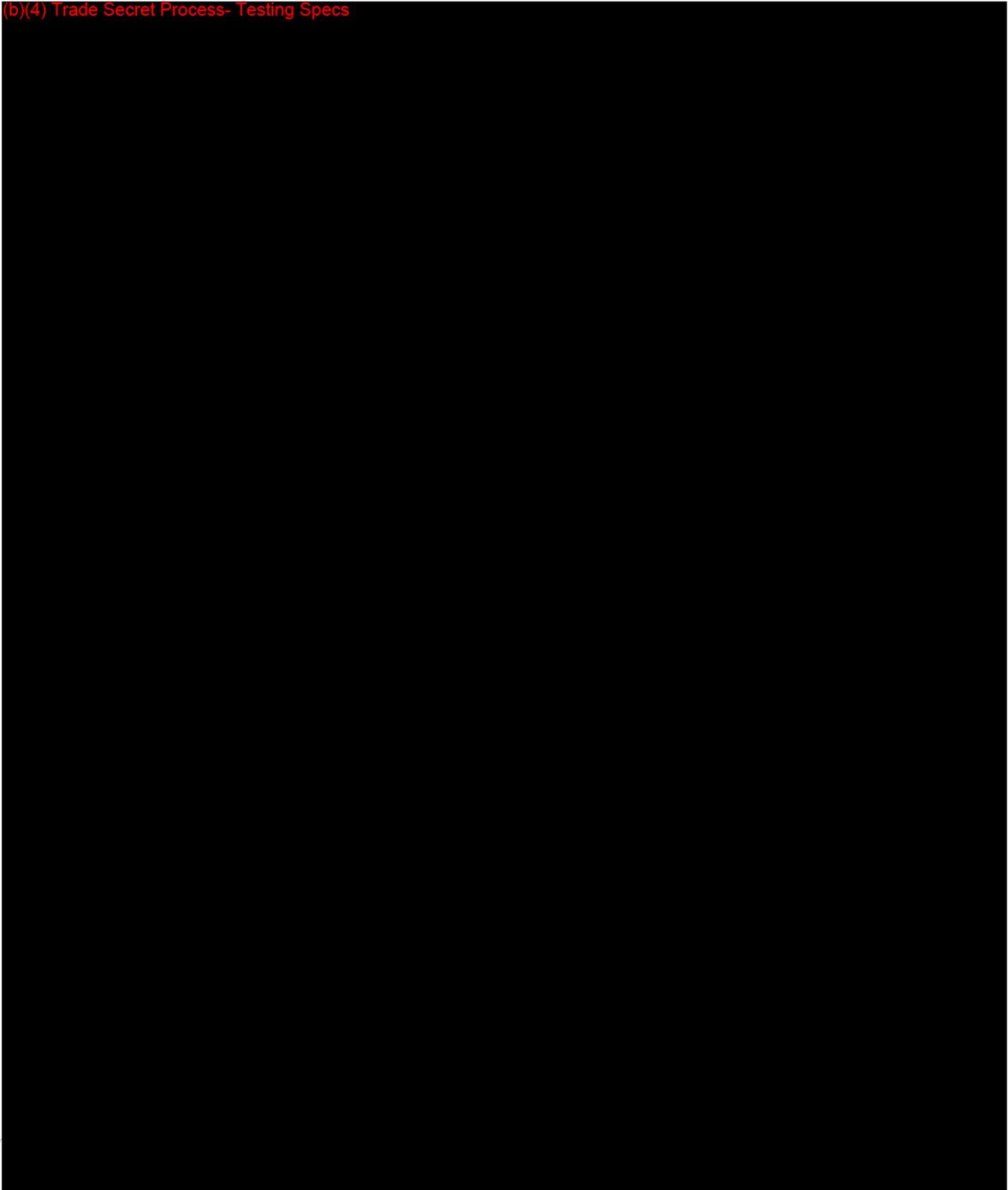
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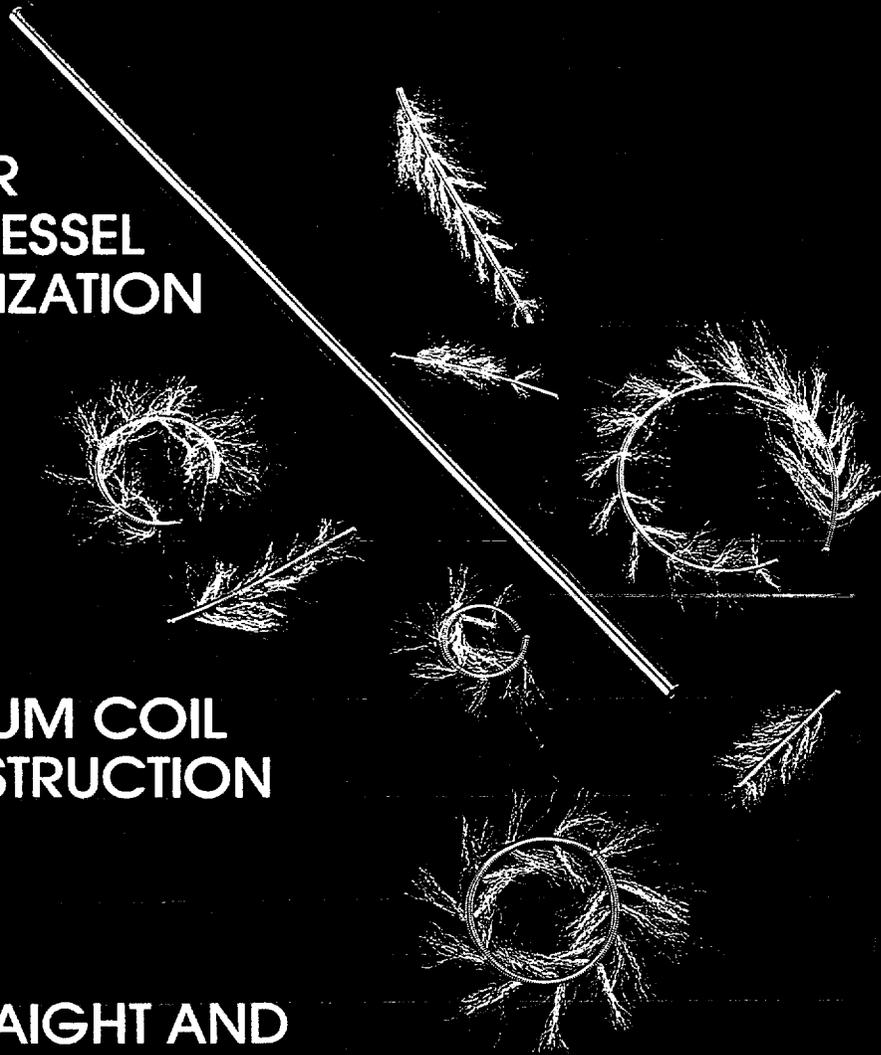
38

HILAL EMBOLIZATION MICROCOILS™

- IDEAL FOR
SMALL VESSEL
EMBOLIZATION

- PLATINUM COIL
CONSTRUCTION

- STRAIGHT AND
CURLED DESIGNS



25 Years

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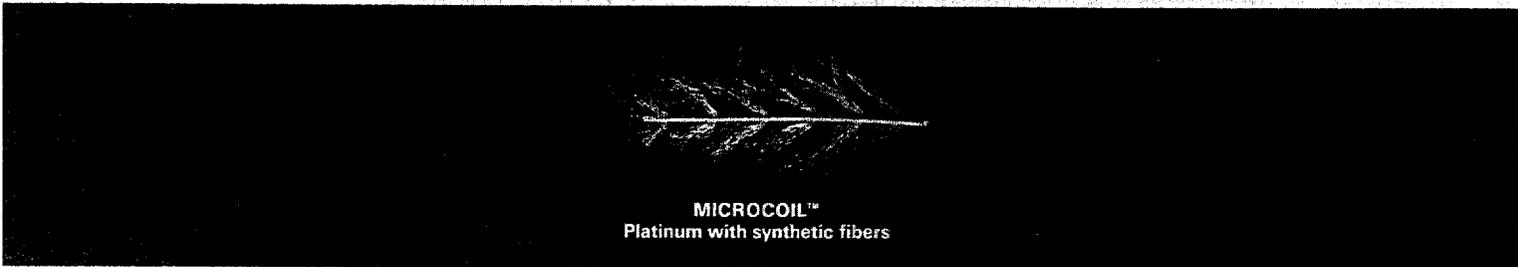
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1965-1988

HILAL EMBOLIZATION MICROCOILS™

STRAIGHT

Used for arterial embolization of selective vessel supply to arterio-venous malformations and other vascular lesions of the brain, spinal cord and spine. Design of the Microcoils™ permits introduction through small, pre-positioned delivery catheters. Unique, straight, non-curling design permits delivery into the target vessel by saline flush after initial advancement through the straightest segment of the catheter using the wire guide. The coils are made of platinum, easily detected radiographically, with spaced synthetic fibers to promote maximum thrombogenicity. Final positioning of Microcoils™ creates a "platinum cast" effect within the vessel lumen. Supplied sterile in peel-open packages. Intended for one-time use.



ORDER NUMBER	Length ¹	Configuration	Remarks
MWCE-18-0.5-0-HILAL	.5 cm	Straight	
MWCE-18-0.7-0-HILAL	.7 cm	Straight	
MWCE-18-1.0-0-HILAL	1.0 cm	Straight	Supplied 2 each per package
MWCE-18-1.5-0-HILAL	1.5 cm	Straight	

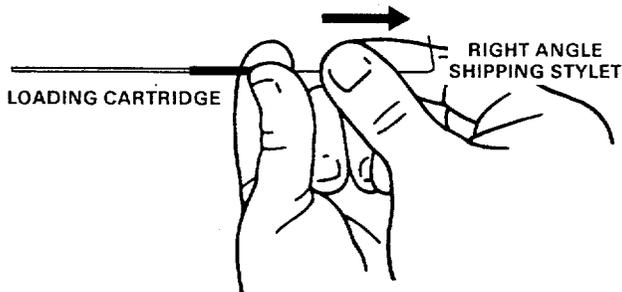
¹Other coil lengths available upon request

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DELIVERY CATHETER AND WIRE GUIDE RECOMMENDATIONS FOR STRAIGHT AND CURLED MICROCOILS™

- Microcoils™ are recommended for use through catheters designed for use with .018 inch (0.46 mm) diameter wire guides and whose inner diameter (ID) does not exceed .027 inch (0.69 mm) diameter. **NOTE:** Cook catheters appropriate for use are non-tapered T3.0 and T3.0S Teflon® catheters.
- Microcoils™ are not recommended for use with polyurethane or polyvinylchloride catheters.
- Wire guides recommended for loading and positioning Microcoils™ are Teflon® coated .018 inch (0.46 mm) diameter with flexible tapered tips. **NOTE:** Cook Order Numbers: **TSFNA-18-180, TSFNB-18-180.**

TO LOAD MICROCOIL™ INTO DELIVERY CATHETER

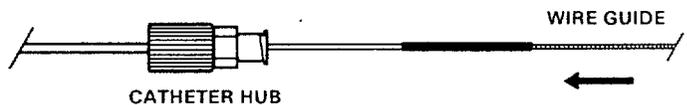


1. Firmly grasp Microcoil™ loading cartridge between thumb and forefinger at point where right angle shipping stylet exits.
2. While maintaining firm finger grip, remove shipping stylet. This will prevent Microcoil™ from exiting cartridge. Verify its position inside cartridge by direct vision.

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3. Position loading cartridge into base of hub of catheter.



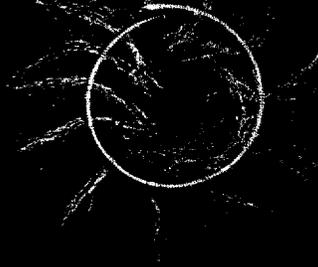
4. Using .018 inch (0.46 mm) diameter wire guide, push Microcoil™ out of loading cartridge and into catheter lumen.
5. Remove loading cartridge.

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HILAL EMBOLIZATION MICROCOILS™

CURLED

Used for arterial and venous embolizations and other vascular lesions of the brain, spinal cord and spine. Design of the Microcoils™ permits introduction through small pre-positioned delivery catheters. Deployment of coils into the vessel lumen is accomplished utilizing standard wire guide pusher techniques. The coils are made of platinum, easily detected radiographically, with spaced synthetic fibers to promote maximum thrombogenicity. Supplied sterile in peel-open packages. Intended for one-time use.



MICROCOIL™
Platinum with synthetic fibers

ORDER NUMBER	Curled Diameter	Length	Configuration	Remarks
MWCE-18-1.0-3-HILAL	3 mm	1.0 cm	Curled	
MWCE-18-1.5-5-HILAL	5 mm	1.5 cm	Curled	
MWCE-18-2.1-7-HILAL	7 mm	2.1 cm	Curled	Supplied 2 each per package
MWCE-18-3.0-10-HILAL	10 mm	3.0 cm	Curled	

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REFERENCES

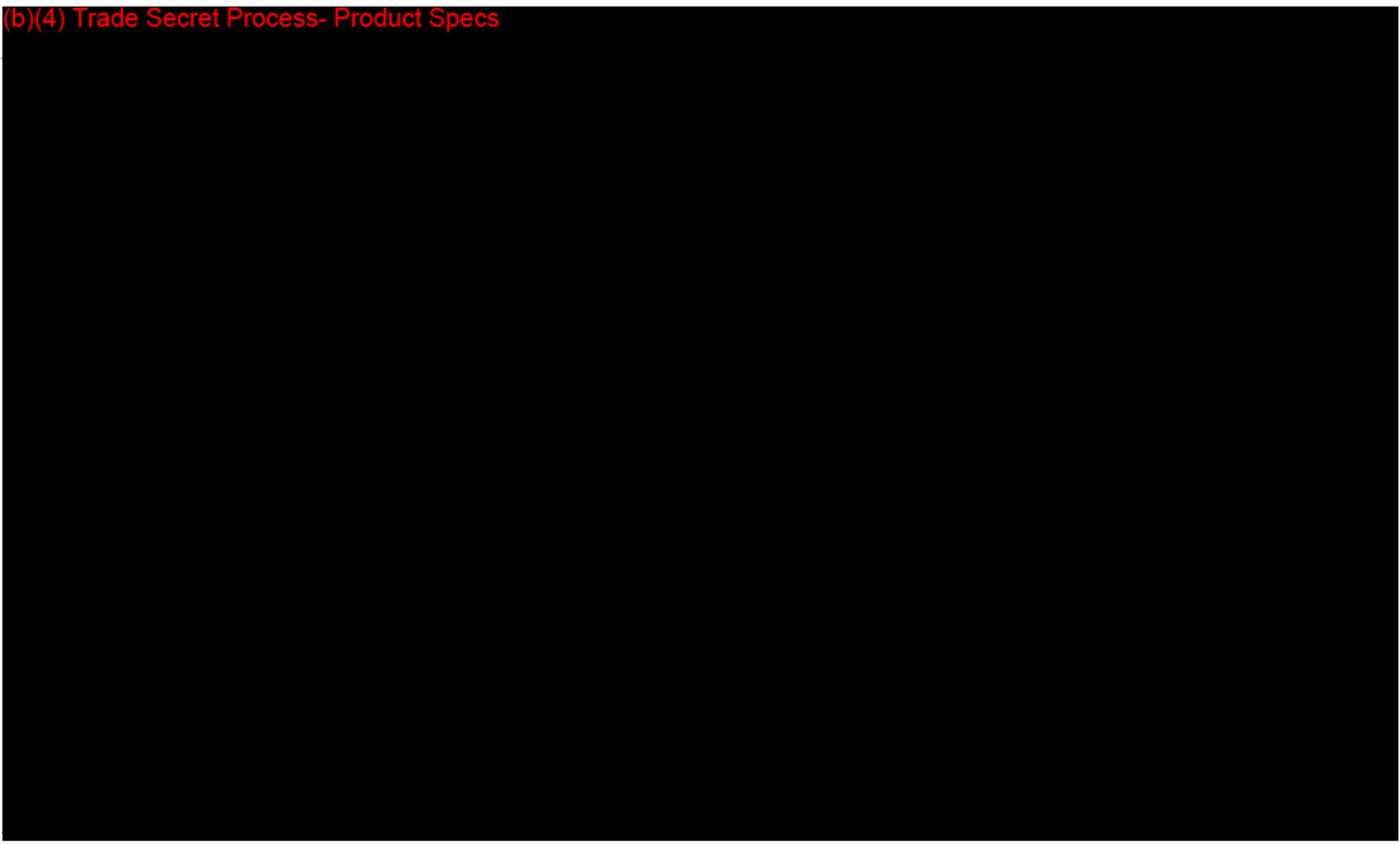
S. Hilal, M.D., Department of Radiology, The Neurological Institute, New York, New York.

S. Hilal, et al: "Synthetic Fiber Coated Platinum Coils Successfully Used for the Endovascular Treatment of Arterio-Venous Malformations, Aneurysms, and Direct Arterio-Venous Fistulae of the Central Nervous System," Scientific paper presented at the 26th Annual Meeting of the American Society of Neuroradiology, Chicago, Illinois, May, 1988.

V. P. Chuang, S. Wallace, C. Gianturco: "A New Improved Coil for Tapered Tip Catheter for Arterial Occlusion," *Radiology*, 135 (1980), 507-509.

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(b)(4) Trade Secret Process- Product Specs

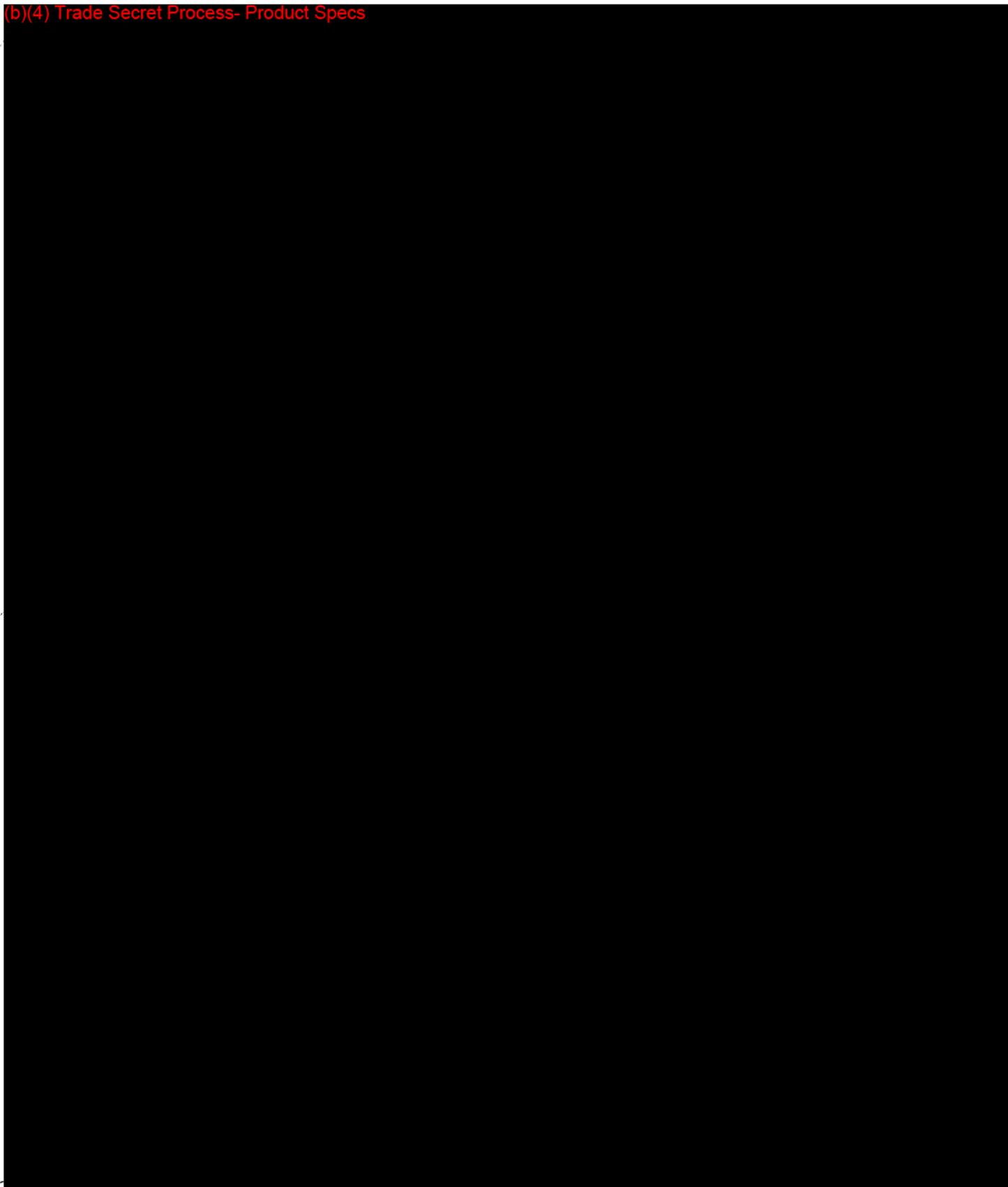


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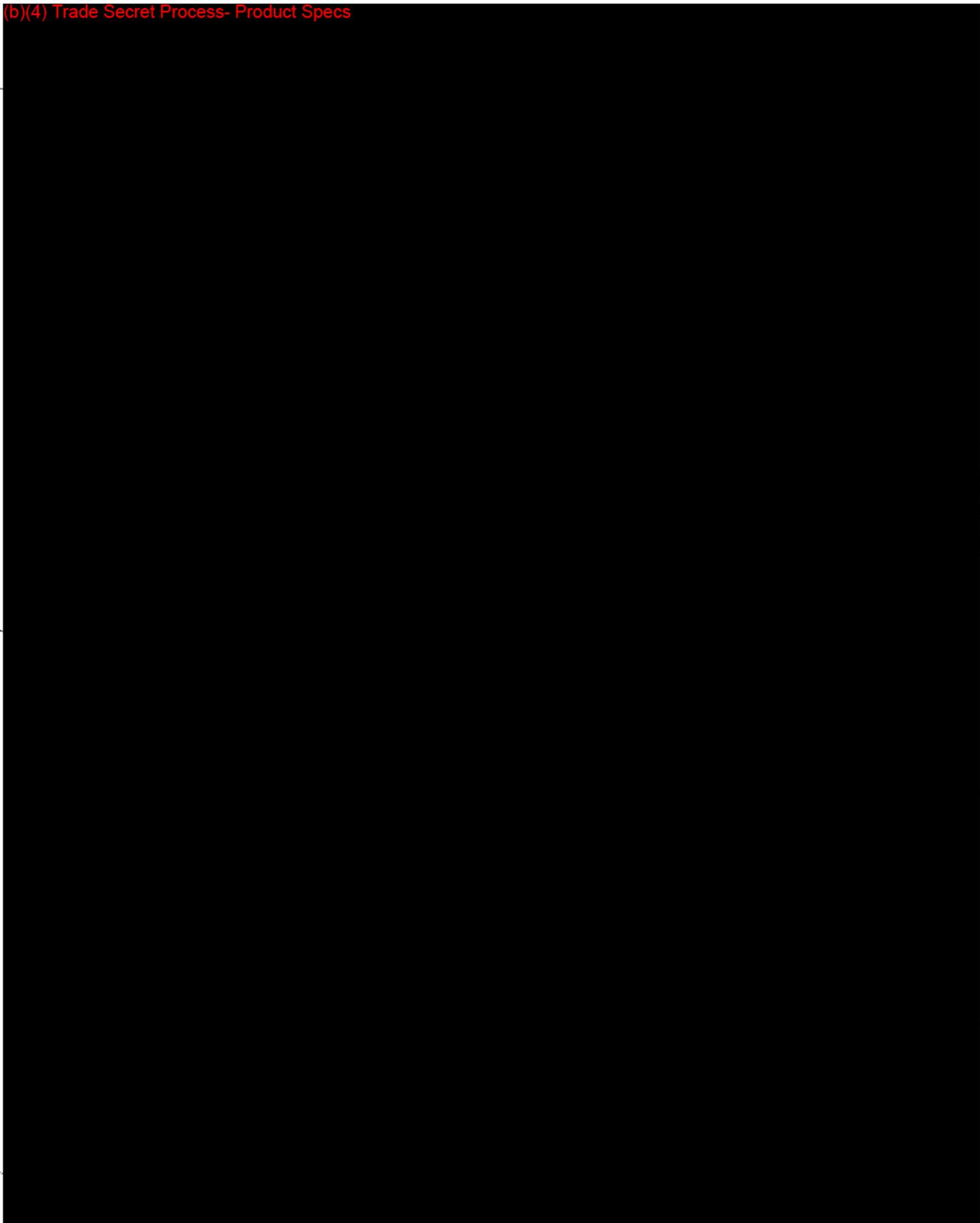


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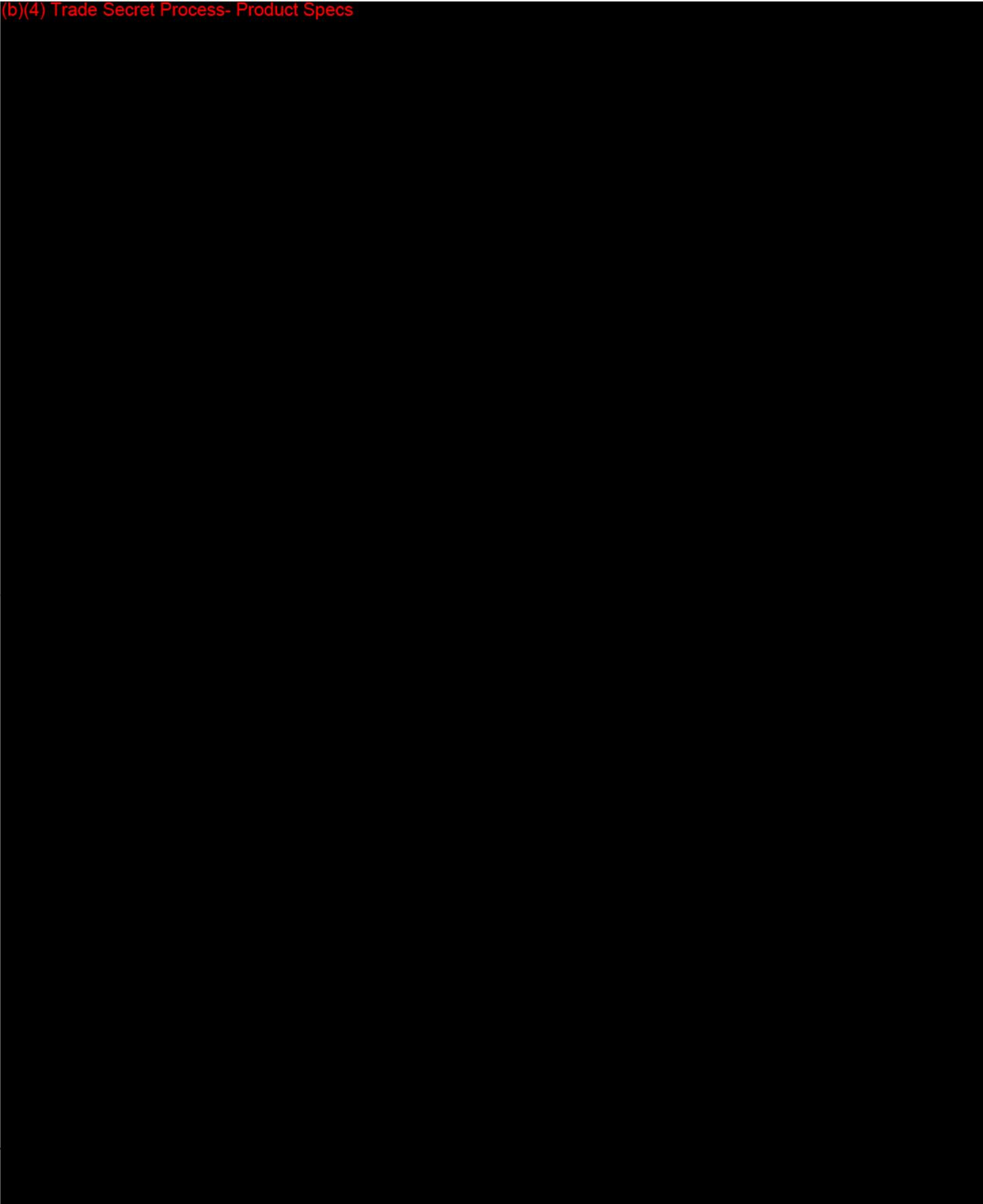


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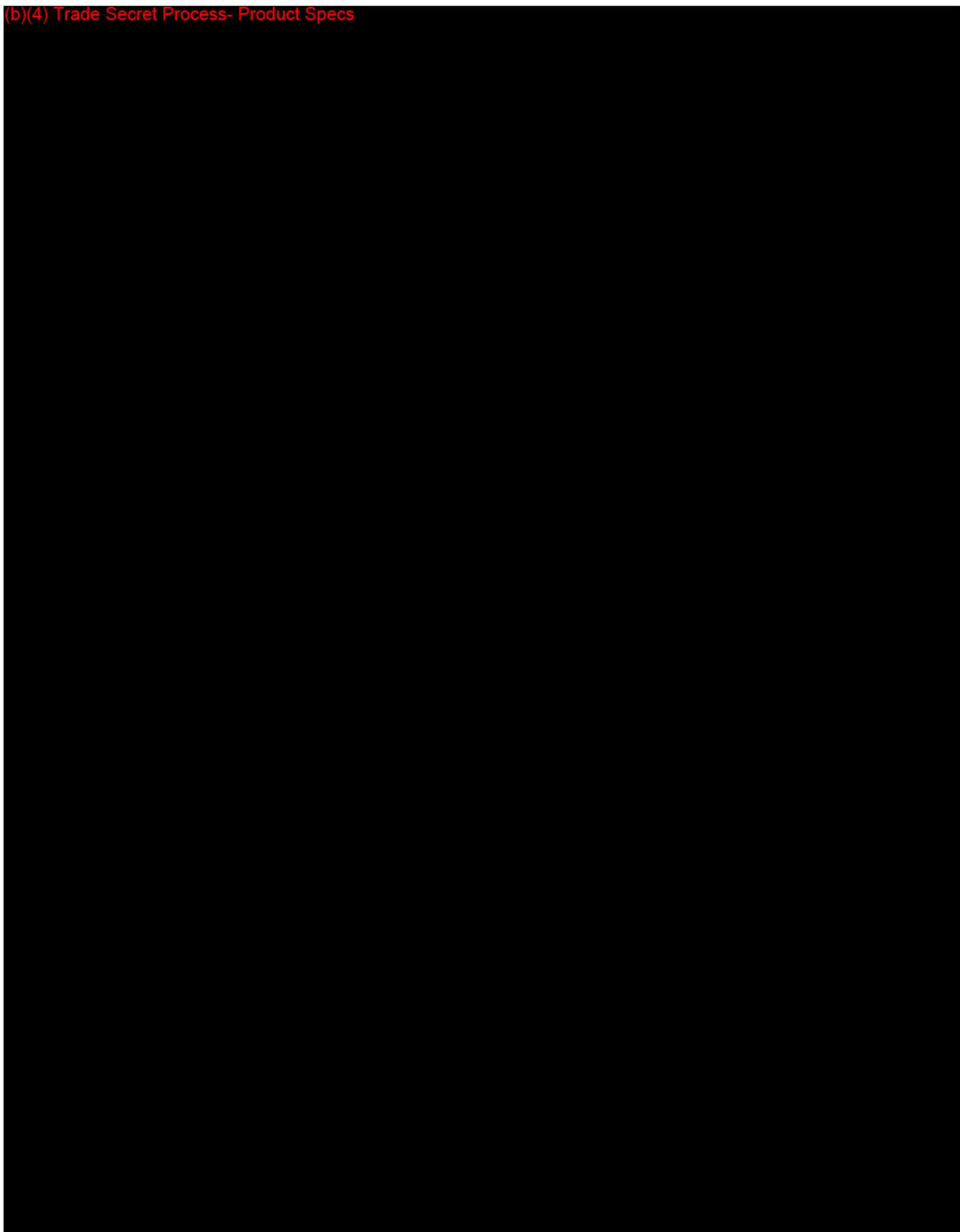
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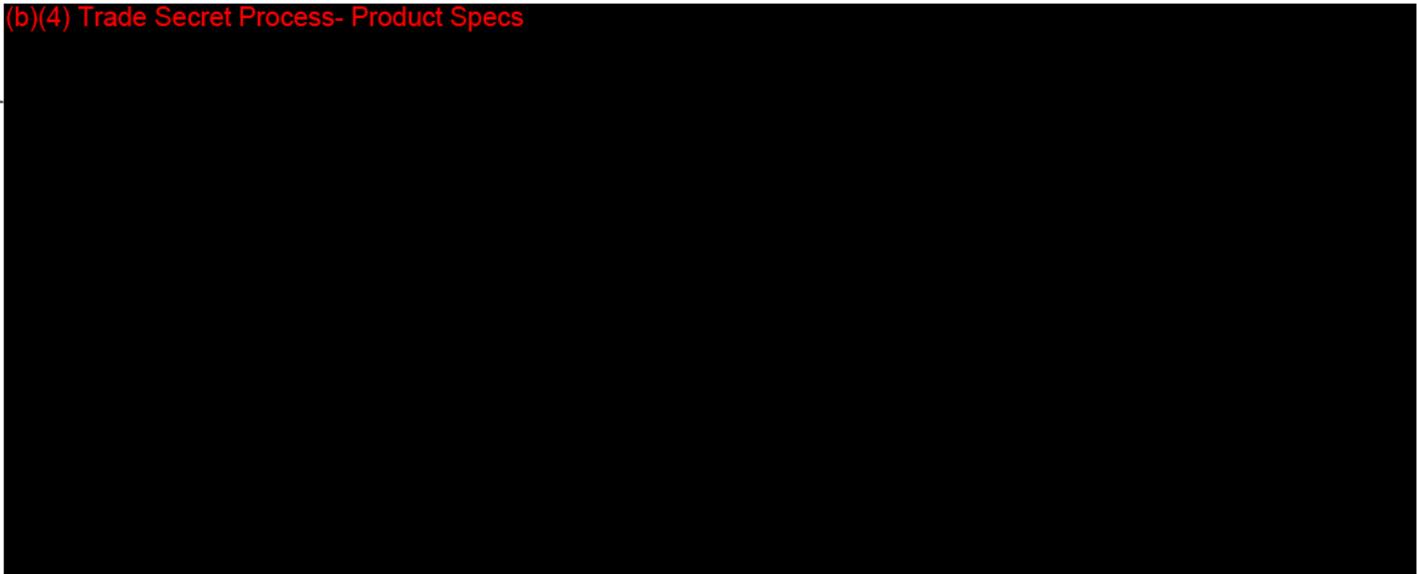
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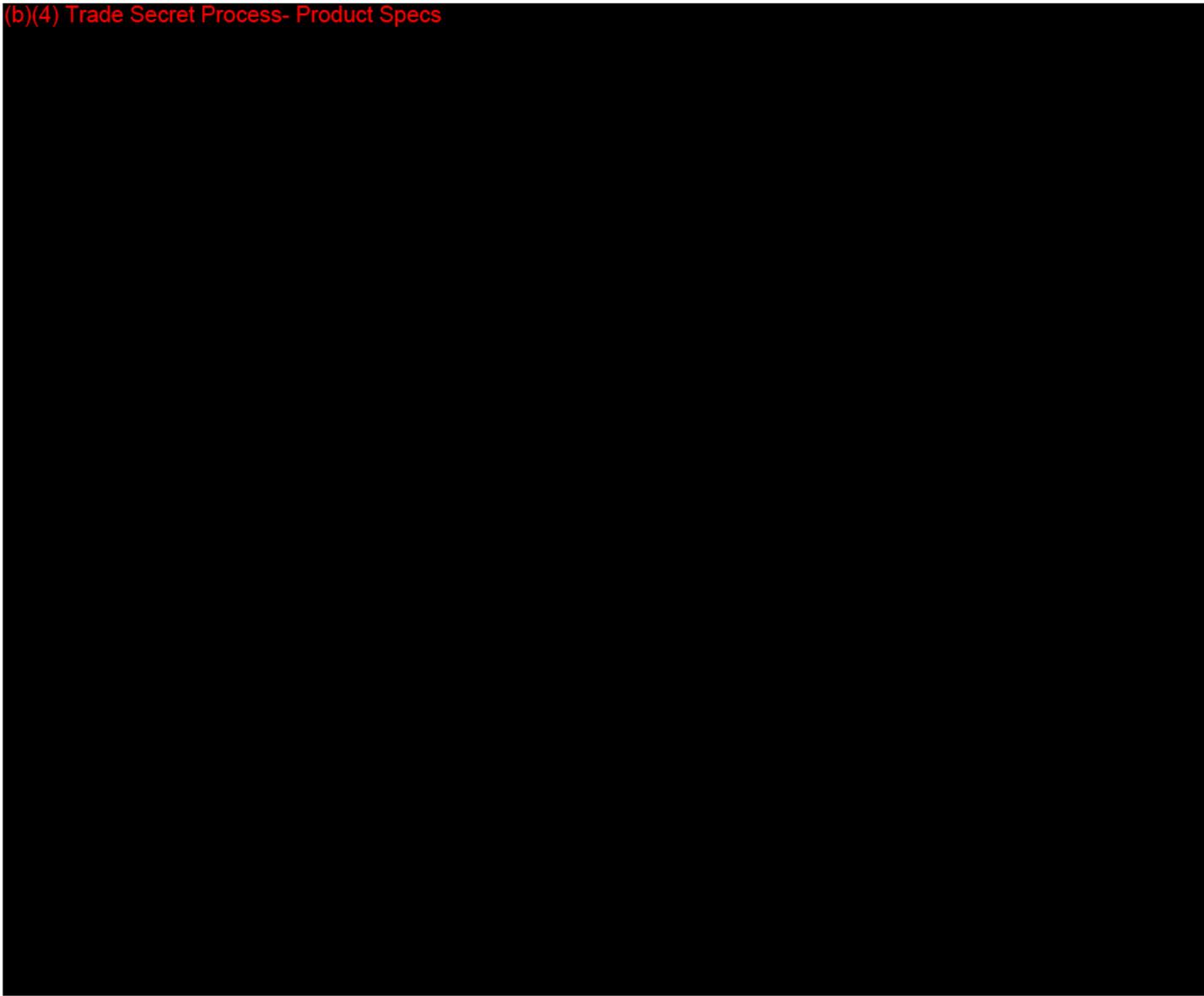


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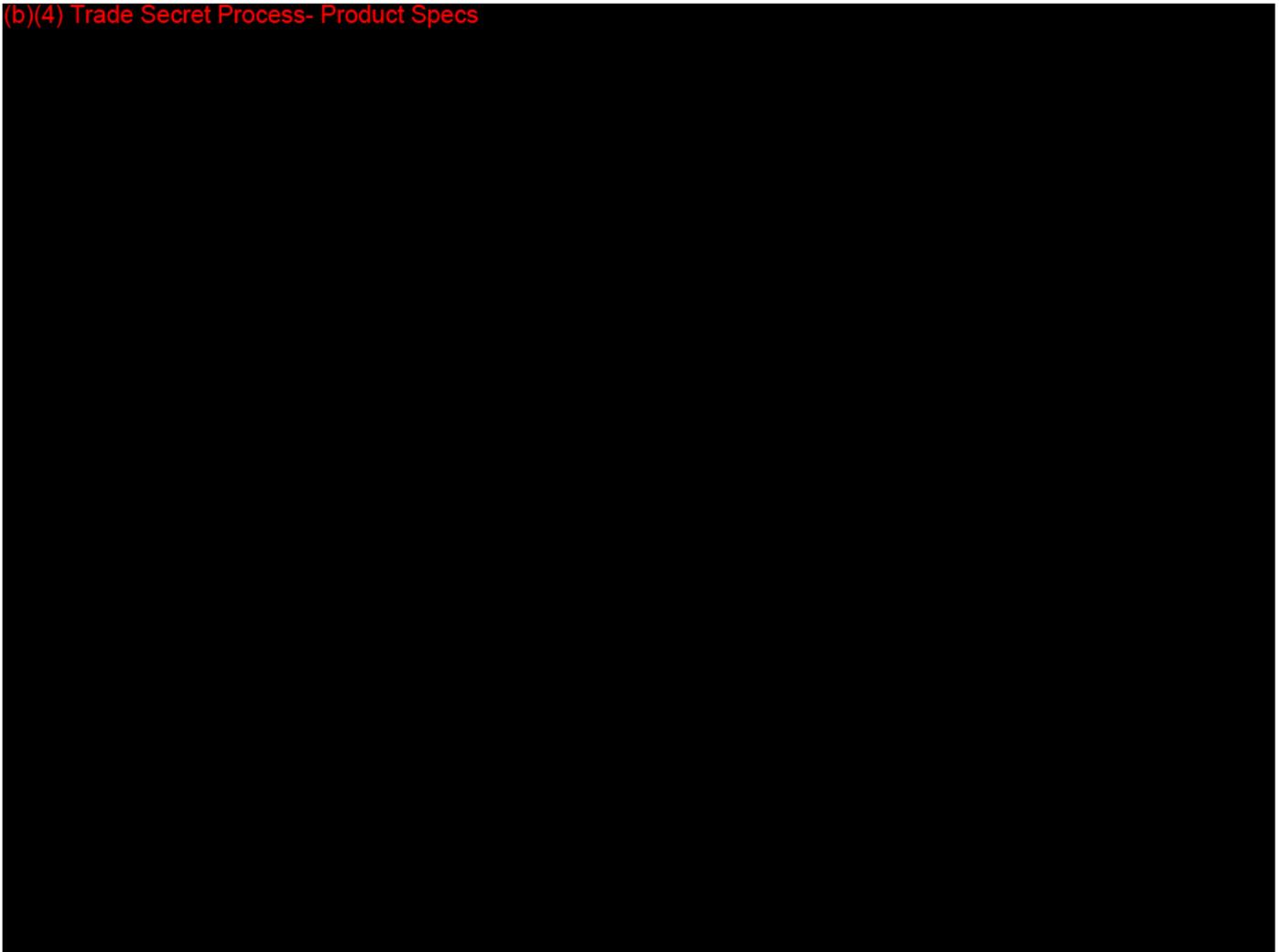


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7. Your submission does not include a discussion of how the rod shaped device can be used in arbitrary lengths as it is offered in your labeling. Please provide information which supports your offer that any length can be used.

The appropriate lengths of the rod-shaped Hilal Microcoil™ are determined by the physician, an experienced angiographer, as indicated by the size and location of the malformation to provide optimum embolization. The straight, rod-shaped Hilal Microcoil™ is available in standard lengths of 0.5, 0.7, 1.0 and 1.5 cm.

Offering other than standard lengths upon request is intended to address the physician who desires a non-standard size. The required length of the rod-shaped coil, determined by the physician, depends on the size and location of the malformation. We believe it is safer to offer non-standard sizes than for the physician to self-manufacture or modify a standard size to obtain the desired size. The offer of non-standard sizes is preferable from the patient's, physician's and manufacturer's perspective and likely from the regulatory safety perspective as well. We believe the range of 0.25 to 2.0 cm is safely supported by the data submitted and represents a reasonable range of available non-standard sizes.

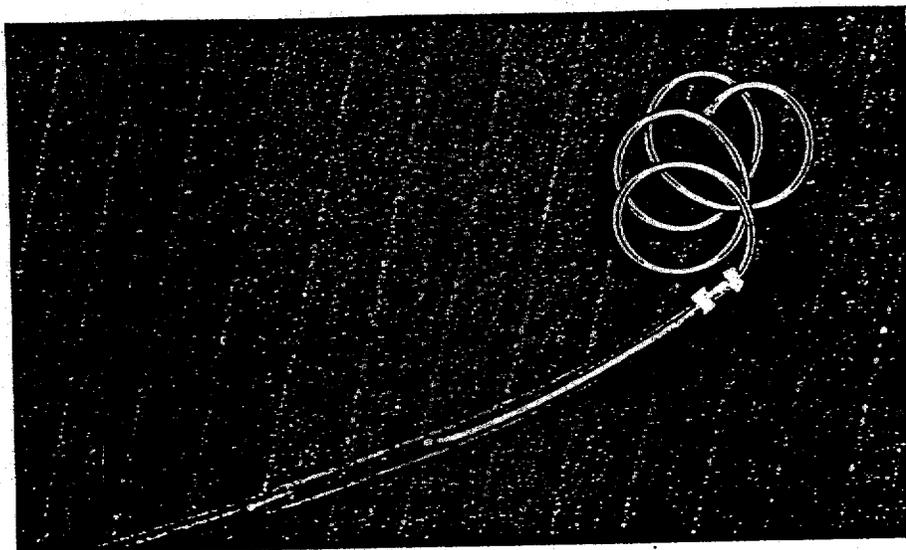
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Appendix I

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COMPLEX HELICAL
PLATINUM COILS
VASCULAR
OCCCLUSION SYSTEM



APPPLICATIONS

- o The occlusion system, used in conjunction with a Tracker®-18 Catheter, allows selective delivery of Platinum Coils to the smallest vasculature. The Platinum Coils are indicated for preoperative vaso-occlusion and site

specific flow reduction of vascular abnormalities in the central nervous system:

- Arteriovenous malformations
- Arteriovenous fistulas

FEATURES

- o Platinum Coils are non-ferromagnetic.
- o Complex helical design reduces dead space evident in single helical coils.
- o Spatial filling of selected vasculature by radiopaque platinum.
- o Polished, soft coil tip lessens likelihood of vessel wall trauma.

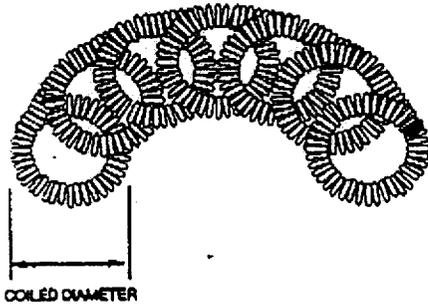
- o Coil Pusher-16 improves control during coil delivery.
- o Laminated polymer surface on pusher reduces friction with the Tracker-18.
- o Radiopaque gold-tipped marker on Coil Pusher-16 allows fluoroscopic visualization.
- o Available in a wide variety of sizes.

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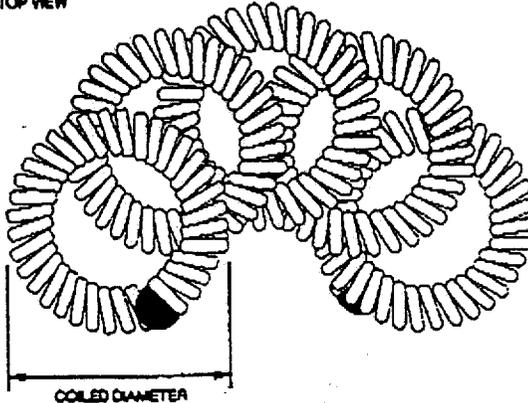
COMPLEX HELICAL
PLATINUM COILS
VASCULAR
OCCCLUSION SYSTEM

TOP VIEW



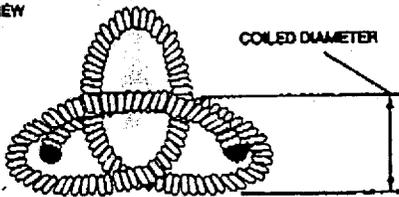
COIL PRODUCT NO. 311024

TOP VIEW



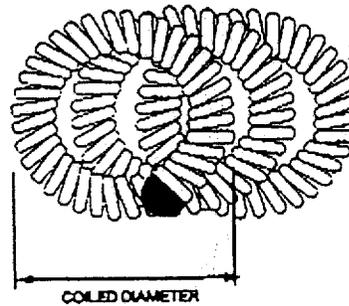
COIL PRODUCT NO. 311046

TOP VIEW



COIL PRODUCT NO. 311022

TOP VIEW



COIL PRODUCT NO. 311043

Drawings are not shown to scale

SPECIFICATIONS

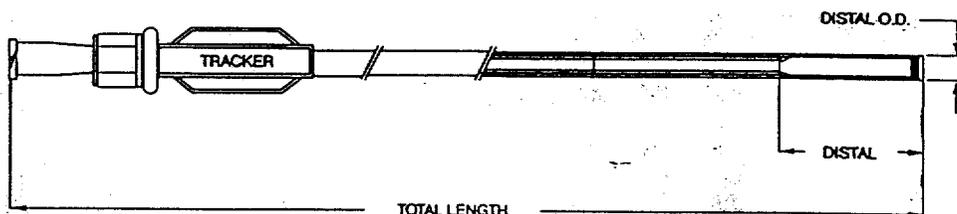
Kit Product No.	Coil Product No.	Coiled Diameter (mm)	Length in Introducer (cm)*
520024	311024	2	4
520046	311046	4	6
520022	311022	2	2
520043	311043	4	3

*Straight length of coil in introducer.



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TRACKER®-18 INFUSION CATHETER



A APPLICATIONS

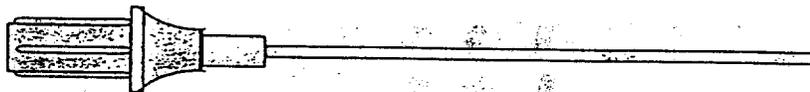
- o Positive access to the smallest vasculature, the Tracker system of microcatheters are essential for:
 - subselective angiography
 - embolization of distal vascular anomalies
 - site specific thrombolytic therapy
 - chemoembolization and drug delivery
 - crossing vascular lesions in tortuous pathways

F FEATURES

- o Most widely used Tracker Infusion Catheter.
- o Coaxial microcatheter may be used with all angiographic/guiding catheters which will accept 0.038 in. guide wire.
- o Radiopaque distal platinum tip for easy visualization under conventional fluoroscopy and digital subtraction angiography (DSA).
- o Available in Vascular Access System kits (VAS).

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ACCESSORIES



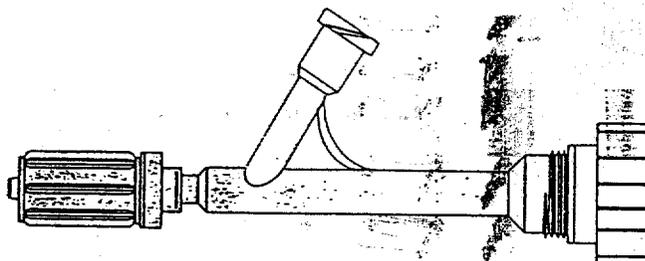
GUIDE WIRE INTRODUCER

- o Facilitates passage of pre-shaped guide wire through Rotating Hemostatic Valve into catheter.
- o Protects guide wire distal platinum coil tip.
- o See system set-up for additional recommendations.



TORQUE DEVICE

- o Pin vise attached to proximal end of guide wire facilitates smooth, accurate positioning of guide wire distal tip.
- o Two piece design configuration.



ROTATING HEMOSTATIC VALVE (RHV)

- o A transparent rotating Tuohy-Borst adaptor with an adjustable valve provides a fluid tight seal between catheters, guiding catheters and guide wires.
- o Allows continuous flush between angiographic catheter and Tracker[®] or between Tracker and guide wire.
- o Inside diameter: 0.054 in./4.1F.
- o See system set-up for additional recommendations.

PRODUCT NUMBER

422290 Guide Wire Introducer for 0.010 in. to 0.018 in. guide wires. Included with all guide wires.

423242 Rotating Hemostatic Valve. Included with all Tracker[®] catheters.



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Platinum Wire: A New Transvascular Embolic Agent

Peter J. Yang^{1,2}
 Van V. Halbach¹
 Randall T. Higashida¹
 Grant B. Hieshima¹

Standard Glanturco and "mini" coils cannot be used with some of the present microcatheter systems. However, occasions arise in which metallic coils would be an ideal embolic agent in a vascular structure accessible only to a tracker (2.2-French) catheter system. We performed nine embolization procedures in eight patients with arteriovenous fistulas using platinum coils as an embolic agent. Fistulas were completely occluded in six of the nine cases. In several cases, platinum wire embolization was augmented with other agents. Complications occurred in two cases, neither resulting in permanent neurologic deficits.

Advantages of using platinum coils include availability, radiopacity, thrombogenicity, biocompatibility, and delivery through microcatheters, specifically the tracker catheter system.

Supraselective catheterization has been facilitated by the development of new microcatheter systems. In particular, the 2.2-French tracker catheter^{*} has proved extremely useful in reaching difficult areas during therapeutic embolization procedures. However, the variety of embolic agents that can be used with this catheter is limited because of its small caliber.

Metallic coil devices have been used for transvascular embolization for years [1-6]. Unfortunately, the tracker catheter is not large enough to accept any of the presently available metal coils.

We have encountered a number of cases in which a metallic coil would be useful as an embolic agent, but the area being embolized was only accessible to catheterization with a tracker system. In all these arteriovenous fistulas (AVFs) we attempted to occlude the fistula by thrombosing the draining sinus or vein, a technique described by Mullian [7]. Small pieces of platinum wire proved useful in these instances. Platinum wire obtained from the tips of guidewires is readily available, very thrombogenic, and can be easily deposited through the tracker catheter system.

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Materials and Methods

The platinum wires were obtained from the distal tips of 0.014-in.[†] and 0.013-in.[‡] steerable guidewires. The tips were cut to lengths of 0.5-1.5 cm with sharp scissors, resterilized, and shaped into a curved or coiled configuration using the same techniques used to form a curve on the tip of a guidewire. The guidewire tip was placed in the desired location by loading the wire into a needle introducer and pushing it through the tracker catheter with a second guidewire (Fig. 1). Multiple platinum wire pieces were placed into the vascular structure, until the desired amount of occlusion was effected.

A total of nine embolization procedures were performed on eight patients with AVFs (one patient with bilateral carotid-cavernous fistulas [CCF] had two separate procedures). Five patients had dural AVFs and three patients had posttraumatic, direct CCFs.

In all cases, the platinum wires were placed into the cavernous sinus, a venous sinus, or a draining vein involved with the fistula. The objective was to either completely occlude the

Received July 28, 1987; accepted after revision October 27, 1987.

¹ Department of Radiology, Division of Diagnostic and Interventional Neuroradiology, UCSF, San Francisco, CA 94143.

² Present address: Magnetic Resonance Imaging, Department of Radiology, University Medical Center, Tucson, AZ 85724. Address reprint requests to P. J. Yang.

AJNR 9:547-550, May/June 1988

^{*} Target Therapeutics.
[†] Advanced Cardiovascular Systems.

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abnormal vascular communication or slow blood flow enough to allow use of other embolic material. In four cases, the wires were used alone. In four other patients embolization was augmented with isobutyl-2-cyanoacrylate (IBCA) (3), and Gianturco "mini" coils (1). Silicone balloons were used in one case in which an internal carotid artery occlusion had to be performed.

Results

The results in our eight patients are summarized in Table 1. In six of the nine cases, there was complete closure of the fistula. Of these cases, two had additional embolization with IBCA and one with "mini" coils. In the two cases with IBCA, the fistulas were so large that platinum wire embolization alone was insufficient. However, it was thought that embol-

ization with liquid adhesives alone was dangerous without first decreasing blood flow through the fistula using the platinum wire.

In two cases, blood flow through the fistula was diminished without complete closure. In one patient, the goal of therapy was to arrest a progressive seventh-nerve palsy associated with erosion of the temporal bone by an extremely large dural AVF (patient 1). After embolization of a selected portion of the fistula, there was improvement in seventh-nerve function. In the other case (patient 4), a left-sided, direct CCF was embolized with platinum wires after balloons failed to completely close the fistula. Postembolization angiography demonstrated markedly decreased flow through the CCF. Because the clinical symptoms resolved, a follow-up angiogram was not obtained.

There were two complications associated with platinum wire insertion. In one case with a CCF (patient 5), placement of platinum wires using a transarterial approach resulted in extrusion of part of a wire through the cavernous sinus into the lumen of the internal carotid artery. Attempts to angioplasty the wire into the sinus with a balloon were unsuccessful and the patient underwent balloon occlusion of the internal carotid artery without complications.

In a patient with a cavernous sinus dural AVF (patient 8), progressive proptosis, pain, and acute blindness occurred during the embolization procedure because of redirection of blood flow toward the thrombosing superior ophthalmic vein. With decreased flow through the AVF resulting from platinum coil embolization, IBCA was injected into the cavernous sinus with obliteration of the fistula. The proptosis resolved with full recovery of vision within 20 min.

Representative Case Reports

Case 1 (Patient 3)

A 62-year-old man presented with bilateral sixth-nerve palsies, left eye chemosis, and bruit of 3 months' duration. Angiography revealed a dural AVF involving the left inferior petrosal sinus with arterial supply from both external carotid arteries, and dural branches arising



Fig. 1.—Placement of platinum coils into cavernous sinus via inferior petrosal sinus. Lateral film shows tracker catheter traversing 7-French catheter in internal jugular vein (arrows) and tracker tip in cavernous sinus (white arrowhead). Multiple platinum coils are already in cavernous sinus. Another platinum wire (small black arrowheads) is in distal tracker and is being pushed by guidewire (large black arrowhead at tip).

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TABLE 1: Platinum Wire Embolizations

Patient No.	Diagnosis	Catheter Route for Platinum Wire	Other Embolic/Delivery Agent/Route	Results
1	Right transverse sinus dural AVF	Transvenous	IBCA/arterial and venous	Diminished flow
2	Left cavernous sinus dural AVF	Transvenous	IBCA/venous	Closed
3	Left inferior petrosal sinus dural AVF	Transvenous	—	Closed
4	Left CCF	Transvenous	—	Diminished flow
5	Left CCF	Transarterial	Balloons/arterial	Carotid occlusion
6	Right CCF	Transvenous	"Mini" coils/venous	Closed
7	Left CCF	Transarterial	—	Closed
8	Left cavernous sinus dural AVF	Transvenous	IBCA/venous	Closed

Note.—AVF = arteriovenous fistula; IBCA = isobutyl-2-cyanoacrylate; CCF = direct carotid cavernous fistula.

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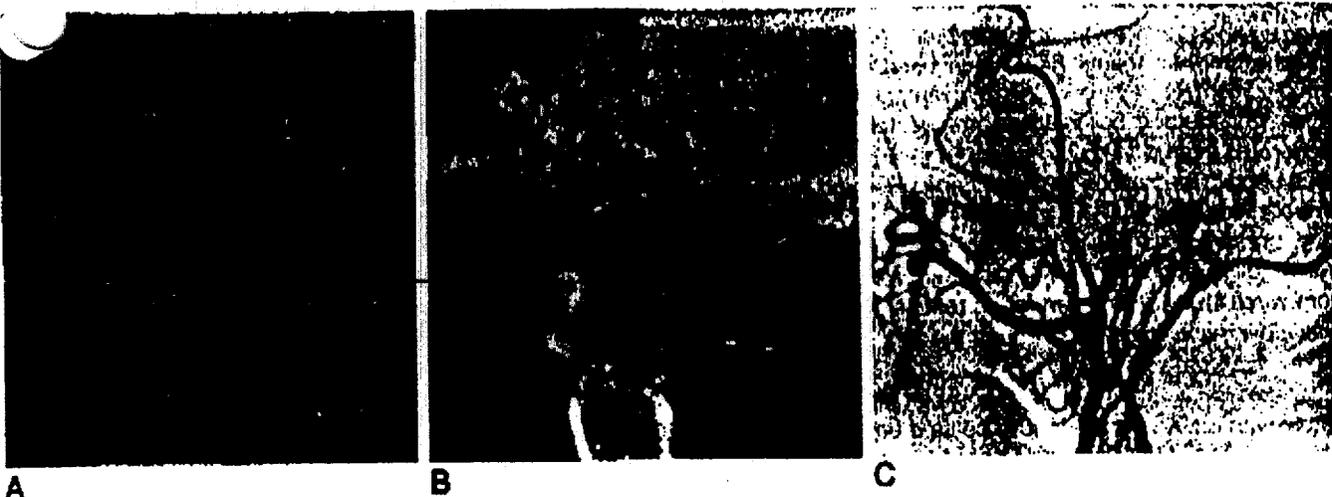


Fig. 2.—A, Left external carotid artery injection, lateral view. Multiple small branches from the external carotid artery fill a dural AVF, which drains into inferior petrosal sinus (arrowheads). Note venous drainage into cavernous sinus and superior ophthalmic vein (arrows).
 B, Postembolization lateral film shows platinum wires in inferior petrosal sinus.
 C, Left external carotid artery injection, lateral view. Postembolization angio-gram reveals almost complete obliteration of AVF. Minimal residual contrast stain is seen near jugular bulb. Injections of internal carotid arteries and right external carotid artery showed no filling of AVF.

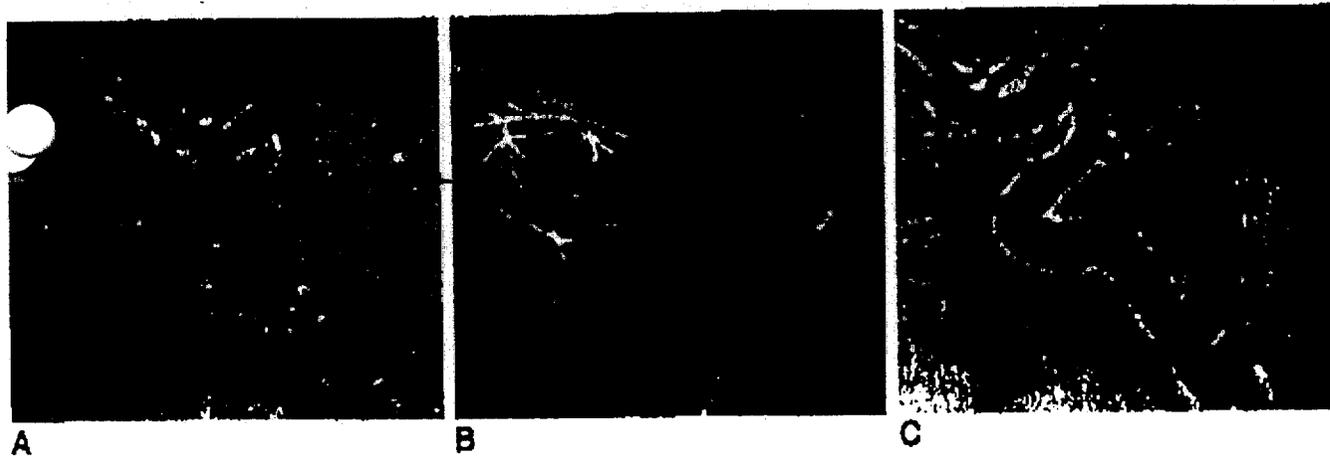


Fig. 3.—A, Left internal carotid artery, lateral view. A direct carotid cavernous fistula has venous drainage into mildly enlarged superior ophthalmic vein (arrowheads).
 B, Postembolization anteroposterior study shows platinum wires in left cavernous sinus. Platinum wires and Glanturco "mini" coils are seen in right cavernous sinus region from prior embolization of right carotid cavernous fistula.
 C, Left internal carotid artery injection, lateral view. Postembolization angio-gram reveals complete obliteration of carotid cavernous fistula.

from the cavernous portion of the left internal carotid artery (Fig. 2A). The predominate venous drainage was into the left cavernous sinuses and an enlarged superior ophthalmic vein.

Ten platinum wires were placed into the left inferior petrosal sinus using a transvenous approach (Fig. 2B). Postembolization angiography revealed virtually complete obliteration of the fistula (Fig. 2C). The patient's bruit and chemosis resolved and there is significant improvement in sixth-nerve function 2 months after the procedure.

Case 2 (Patient 8)

A 20-year-old woman who was involved in a motor vehicle accident presented with right proptosis and a bruit. Angiography disclosed a

right carotid-cavernous fistula. Balloon embolization was unsuccessful because of the small size of the arterial tear; thus, a transvenous approach was used to close the fistula using platinum wires and Glanturco "mini" coils. The platinum wires were used to occlude the cortical venous drainage of the fistula, which was only accessible via a tracker catheter. A 3-French Teflon catheter was used to place Glanturco "mini" coils in the remainder of the cavernous sinus, with successful occlusion of the fistula. Because of persistent bruit, a second CCF was discovered on the left side (Fig. 3A). Again, balloon embolization was unsuccessful. A transvenous approach was also attempted without success. Finally, a tracker catheter was used to place platinum wire into the left cavernous sinus through the fistula via the internal carotid artery (Fig. 3B). Postembolization angiography disclosed complete occlusion of the CCF (Fig. 3C).

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Discussion

Many embolic agents have been used for transvascular embolization, each having their advantages and disadvantages [8]. Metallic coil devices are useful for occluding a moderate to large vascular structure [1-6]. Coils have also been used in the past as an aid to particulate and liquid-agent embolization [9].

At present, it is not possible to introduce a standard or "mini" coil through the tracker catheter. We have used platinum wires instead, with very good results. In all cases, there was a decrease in the flow through the AVF and in four cases there was virtually complete occlusion without the help of other embolic agents. In three cases, complete closure of the fistula with IBCA was thought to be safe only after the blood flow through the fistula was decreased using platinum wires.

Platinum wires were used because of their thrombogenicity, radiopacity, availability, and biocompatibility [10-12]. Thrombogenicity of metal can be enhanced by using an electrical current [13, 14], by combining the wire with fabric strands [15], or by "packing" multiple wires into the vascular structure [16]. ~~Using the tracker system, the last option is the most feasible.~~

We encountered two complications as a result of this technique. In the first patient, extrusion of a small piece of wire represented a potential nidus for thrombus formation. Thus, balloon occlusion of the internal carotid artery was performed. Extrusion of wire is also a problem that may occur with coil insertion [17]. In fact, most of the technical pitfalls with Gianturco coils also apply to platinum wire embolization. In the second patient, proptosis and temporary blindness occurred during the procedure. This was probably caused by redirection of blood flow toward the superior ophthalmic vein, as other routes of venous drainage were being blocked by platinum wire embolization. The sudden, dramatic clinical change necessitated prompt closure of the fistula using IBCA.

In summary, the tracker system has enhanced our ability to catheterize areas that were previously inaccessible. Platinum guidewire tips can be used with this catheter system in a manner similar to metal coil devices. We have found this embolic agent particularly useful in occluding the cavernous sinus or a venous sinus when treating arteriovenous fistulas.

ACKNOWLEDGMENT

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Histopathological Evaluation of Materials Implanted in the Cerebral Cortex

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Summary. Histopathological changes of the cerebral cortex in response to small, penetrating metal and non-metal implants were analyzed by means of light and electron microscopy. The needle-shaped implants were left in place during all stages of histological preparation and embedded in plastic together with the cortex. Changes of the brain-implant boundary were classified as non-reactive, reactive, or toxic, according to the reactive cellular constituents. Among the non-reactive materials were several plastics and metals such as aluminum, gold, platinum, and tungsten. The boundary of these implants displayed little or no gliosis and normal neuropile with synapses within 5 μm of the implant's surface. The boundary of reactive materials such as tantalum or silicon dioxide was marked by multinucleate giant cells and a thin layer (10 μm) of connective tissue. Toxic materials such as iron and copper were separated from the cortical neuropile by a capsule of cellular connective tissue and a zone of astrocytosis. Cobalt, a highly toxic material, produced more extensive changes in the zones of connective tissue and astrocytes. These results indicate that a variety of materials are well tolerated by the brain and could be used in the fabrication of neuroprosthetic devices.

Key words: Cerebral cortex — Brain implants — Reactivity — Toxicity — Biocompatibility — Neuroprostheses.

Animal studies have demonstrated the feasibility of implanting electrodes into the brain for long periods to stimulate nerve cells or record electrical activity (Delgado et al., 1961; Hess, 1932). Penetrating electrodes implanted in humans to monitor electro-

encephalographic activity and to stimulate the brain to identify epileptogenic foci have been well tolerated (Dodge et al., 1955; Heath, 1954; Ramey and O'Doherty, 1960; Spiegel and Wycis, 1961; Walker and Marshall, 1961). Thus it has been assumed that penetrating electrodes produce a negligible amount of damage and that no appreciable histological alterations occur in nearby nerve cells when little or no electrical current is passed.

We undertook the current investigation to determine the long-term effects of a variety of materials that might be used to fabricate cortical stimulating electrodes constituting part of neuroprostheses for the blind (Brindley and Lewin, 1968; Dobbelle et al., 1974, 1976; Dobbelle and Mladejovsky, 1974) and deaf (Dobbelle et al., 1973). Although surface electrodes will probably be used in these devices, we chose needle-shaped materials resembling penetrating electrodes for analysis because they can be apposed directly to parenchymal nervous tissue without meningeal intervention and because they represent a "worst case" situation; i.e., they are in direct contact with neurons and are not buffered by cerebrospinal fluid. The current study did not consider the effects of electrical stimulation, but we are now investigating this question.

Studies relying on conventional techniques have revealed an inconsistent pattern of reactive change related to mechanical trauma during implantation or to the materials used to fabricate the electrodes (Collias and Manuelidis, 1957; Robinson and Johnson, 1961). Although Collias and Manuelidis observed a cellular capsule, loose connective tissue, and a dense zone of astrocytes, it is unclear whether these changes were caused by trauma or by the materials used. When Fischer et al. (1957, 1961) and Delgado (1961) introduced metallic and plastic-coated implants into the brains of animals, they observed few changes near

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Table 1. Summary of Histopathological Changes Surrounding Cortical Implants

Reactivity	Material	Type and/or Composition	Number of needles implanted	Duration of implants (days)	
<i>Non-reactive</i>	Aluminum	Trace of iron ^b	16	132-190	
	Alumina ceramic ^c	Sintered aluminum oxide: 96% alumina, 4% silica	6	59-215	
	Gold ^d	99.9%	23	89-134	
	Platinum	100% ^b	14	56-196	
	Polyethylene ^e	Hifax, high-density type	9	74-202	
	Polypropylene ^e	Profax	10	102-223	
	Silicon	Single crystals doped with phosphorus at concentrations of 10 ¹⁸ P atoms/cm ³ ; resistivity = 0.005 ohm-cm	19	88-421	
	Teflon FEP ^f		9	104-211	
	Teflon FEP ^f	Type C20, chemically bondable	6	67-92	
	Teflon FEP ^f	Modified Penntube II SMT	6	67-92	
	Teflon TFE ^f	High-purity sample	12	104-222	
	Tungsten	100% ^b	12	61-190	
	<i>Reactive</i>	Araldite	Epoxy plastic resin Durcupan ACM, Fluka AG ^h containing 0.1% methylene blue dye, Ehrlich 671 ⁱ	62	50-723
		Silicon dioxide	Pyrex	14	59-62
Teflon TFE ^f		Type I with sodium-ammonia surface etching for adhesion	6	72-88	
Tantalum		100% ^b	18	63-418	
Gold-silicon dioxide passivated micro-circuit ^j			27	130-197	
Molybdenum		100% ^b	18	61-227	
Nichrome		80% nickel, 19% chromium, 0.5% iron ^b	12	105-221	
Titanium dioxide		100% ^b	4	104-190	
Teflon TFE ^f		Penntube I, shrinkable	9	67-88	
<i>Toxic</i>		Silastic RTV	Industrial grade, Type D for mold making (vulcanizes at room temperature) on gold wire. Dow Corning	3	88-210
	Germanium	Electrically active elements, less than one part per billion	6	139-220	
	Silver	100% ^b	12	125-219	
	Iron	95.5% iron, 0.5% manganese ^b	10	132-188	
	Copper	100% ^b	12	133-192	
	Cobalt	Cobalt powder, form 309 ^h , and gelatin, USP lot 3139x ^l , mixed according to Fischer et al. (1967, 1968)	62	72-553	

^a 0 = absent, + = occasionally present, ++ = often present, +++ = usually present

^b Method of analysis: ARL electron microprobe

^c Stratamet Ceramic Corp., Redwood City, Calif.

^d Wilkinson Co., Westlake Village, Calif.

^e Hercules, Inc., Wilmington, Del.

^f E. I. DuPont de Nemours & Co., Wilmington, Del.

^g Penntube Plastics Co., Clifton Heights, Pa.

^h Chemische Fabrik, 9470 Buchs, Switzerland

ⁱ Chroma Gesellschaft, Stuttgart, Germany

^j Wise et al., 1970: Integrated Circuit Laboratory, Stanford University, Stanford, Calif.

^k Matheson Coleman & Bell, Norwood, Ohio

^l J. T. Baker Chemical Co., Phillipsburg, N. J.

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the insulated implants but "noticeable damage and necrosis" in the vicinity of metals such as silver and copper. Other investigators (Baleyrier and Quoex, 1975; Chusid and Kopeloff, 1967; Dymond et al., 1970; Wilder et al., 1972) subsequently confirmed these findings using conventional histological procedures and ultrastructural techniques to evaluate the effects of silver, cobalt, and other metals.

Schultz and Willey (1976) described a sheath containing foreign body giant cells around metal electrodes coated with Epoxylite. Their ultrastructural studies confirmed the lack of direct contact between passive electrodes and central nervous tissue but did not consider factors governing the development of the capsule. An investigation of histopathological changes in nervous tissue in the vicinity of small in-dwelling

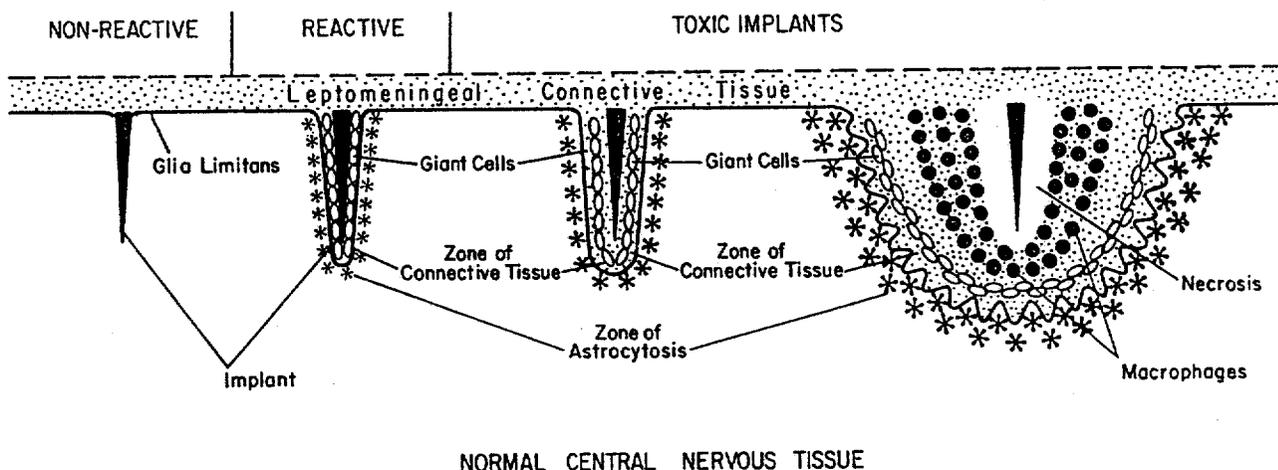


Fig. 1. Summary diagram illustrating the histopathological changes around non-reactive, reactive, and toxic implants. The zones of astrocytosis (asterisks) and connective tissue (stippled areas) vary in size in proportion to the implant's reactivity. Giant cells (white circles) and macrophages (black circles) are restricted to the zone of connective tissue

and needles of one material were carefully inserted into the brain with watchmaker's forceps (Fig. 1). The skin was then closed with wound clips, and the animals were allowed to survive from 50 to 723 days. Silicon dioxide and Araldite needles were also implanted in young adult rats weighing 150 g anesthetized with chloral hydrate and ether.

One hour before sacrifice, the animals were injected with 1000 units of heparin. They were then anaesthetized with Innovar and ether, respired, and perfused through the heart with 0.12 M phosphate-buffered fixative (pH 7.4) containing 1% paraformaldehyde and 1% glutaraldehyde (Wuerker and Palay, 1969) or with 0.1 M cacodylate-buffered fixative (pH 7.4) containing 4% paraformaldehyde and 0.5% glutaraldehyde (Matthews and Kruger, 1973). Four hours after perfusion, the brain was partially exposed and the head was immersed in cold phosphate- or cacodylate-buffered fixative for 18–24 h.

Elongate blocks of tissue with the implants in the center were carefully removed without damaging the brain-implant boundary. A rim of cortex 0.5 mm wide surrounded each implant, yielding a block with final dimensions of approximately $4 \times 1.5 \times 2.0$ mm. The blocks were washed in buffered sucrose solution, immersed in 2% osmic acid for 4–5 h, dehydrated in ethanol and acetone, and embedded in Araldite (Fluka). The boundary was then sampled using one of the following techniques. 1. Relatively soft materials such as aluminum and gold were left in place and sectioned together with the cerebral cortex. 2. The exposed surface of harder materials was carefully trimmed to a narrow strip along the boundary with either a stainless-steel razor blade or a high-speed dental drill. Although the glass knife was often damaged during sectioning, the boundary containing the tissue usually remained intact. 3. Extremely hard materials were partially exposed by removing portions of the tissue and then breaking the implant away from the block with fine forceps. In well-polymerized blocks, this procedure left an intact brain-implant boundary that could be cut with a glass or diamond knife.

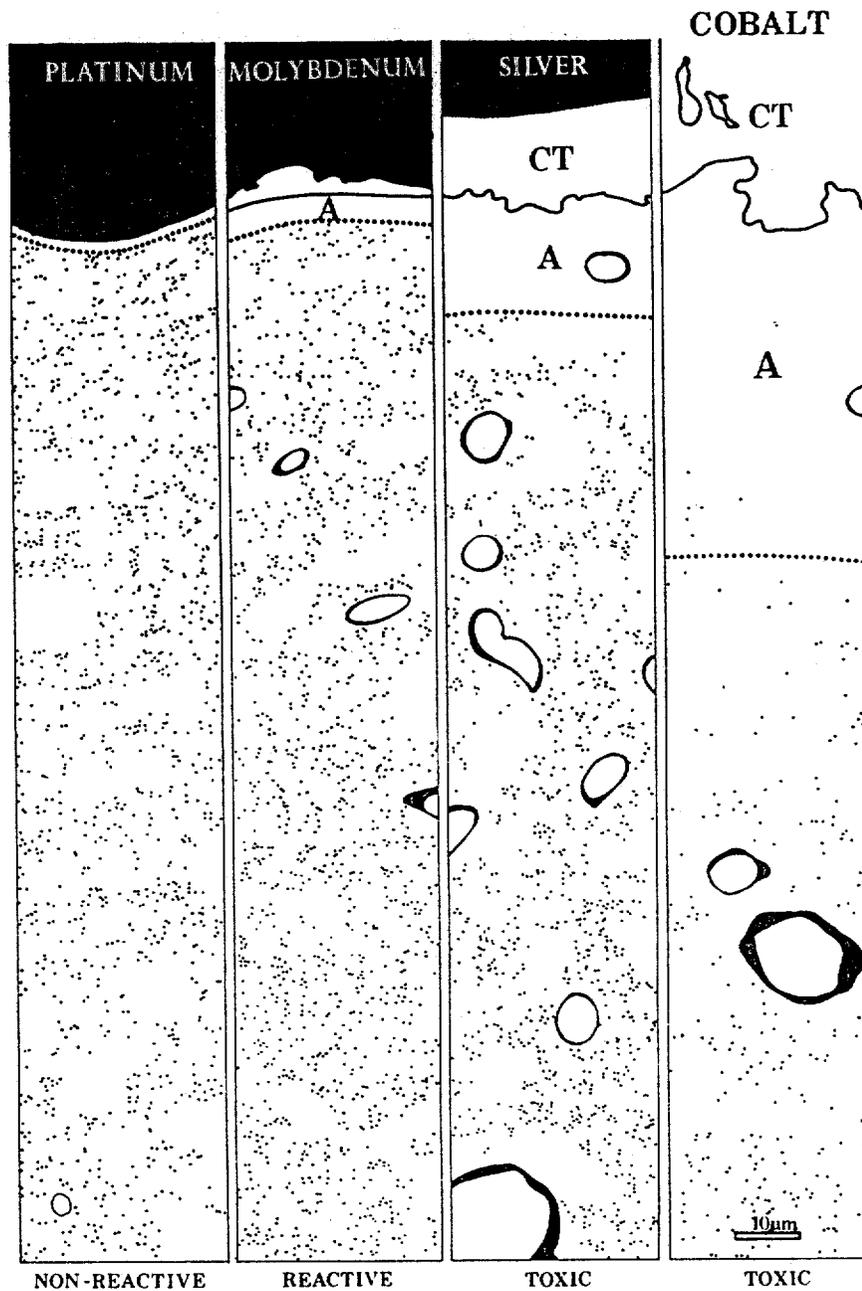
Sections were taken from all blocks approximately 1 mm beneath the pial surface and, when necessary, from deeper and more superficial levels as well. Semithin (1.0 μ m) sections were mounted on glass slides and stained with a 1% methylene blue-1% borax solution. Ultrathin (0.06 μ m) sections were mounted on formvar film in one-hole (1 \times 2 mm) grids and stained with uranyl acetate and lead citrate. Thirteen materials—aluminum, Araldite, cobalt,

copper, germanium, iron, molybdenum, platinum, polyethylene, silastic RTV, silver, Teflon TFE, and Teflon FEP—were examined with the electron microscope.

Histopathological changes visible in plastic sections by light microscopy at high magnification (1000 \times) and by electron microscopy of companion sections were evaluated with reference to each type of reactive cell in both central nervous tissue and the connective tissue capsule. Estimates of the degree of change in each of these elements in the vicinity of implants with reactive alterations were based on comparison with boundary conditions of non-reactive implants. The changes that occurred were arbitrarily assigned a value on a three-point scale according to the degree of change visible in areas of minimal reaction. The findings from such evaluations, which involved several implants of the same material, were then compiled and used to prepare Table 1. The spectrum of reactive change apparent in Table 1 was used to classify implants as non-reactive, reactive and toxic and the general pattern characteristic of each was depicted qualitatively in a summary diagram (Fig. 1).

Results

Table 1 ranks the materials in order of increasing reactivity, according to the cellular constituents of the connective tissue capsule and changes in central nervous tissue. This classification is based on observations of semithin and ultrathin sections in which the implant remained in contact with the cortex during all preparatory procedures. The variability encountered at the brain-implant boundary of a particular material was attributable primarily to mechanical trauma during implantation (Stensaas and Stensaas, 1976) and, to a lesser extent, to ongoing damage caused by differential movement of brain and implant when the implant extended beyond the cortical surface and contacted the dura mater. To rule out the effect of this variability on the grading system used for histopathological analysis, only areas of minimal



Schematic representation of synapses (small black dots) and blood vessels (circles) in cortex surrounding non-reactive, reactive, and toxic implants (solid black). The solid line marks the boundary between the zone of connective tissue (CT) and the cortex. Note the reduction of synapses in cortex surrounding toxic implants: this is correlated with an increasingly wider zone of astrocytosis (A). Left to right: platinum (196 days), molybdenum (227 days), silver (219 days), and cobalt (72 days)

histological change were analyzed. Thus the data in Table 1 represent *minimal* reactive alterations observed around each type of implant. It should be emphasized that all implants of a particular material showed a consistent pattern of change.

The principal changes in cortex surrounding non-reactive, reactive and toxic implants are summarized schematically in Figure 1. Whereas normal central nervous tissue extended to the surface of non-reactive implants, zones of astrocytosis and connective tissue surrounded reactive and toxic implants. Although the and complexity of these zones varied, the same

basic pattern was typical of viable tissue around all reactive and toxic materials. In addition, however, a zone of necrosis surrounded cobalt.

Figure 2 illustrates the distribution of synapses in neuropile around the different types of implants, based on an analysis of EM photomontages. The gray matter within 10 µm of non-reactive and reactive implants showed a normal incidence of synapses. However, the cortex surrounding toxic implants showed a reduced incidence of synapses and an increased number of blood vessels. Similar patterns of synaptic distribution were observed in ultrathin sam-

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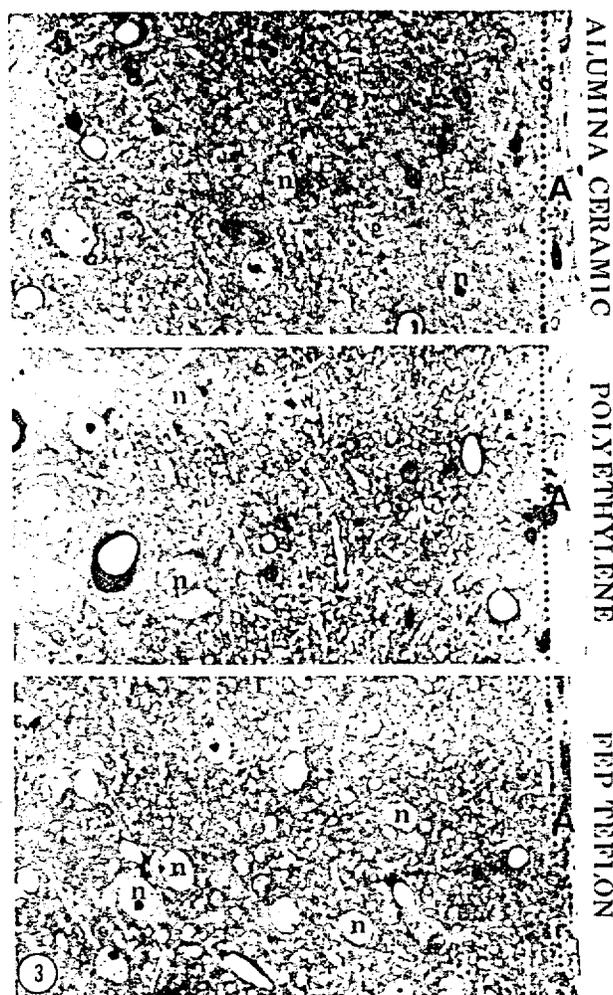


Fig. 3. Brain-implant boundary of non-reactive ceramic and plastic implants. Cerebral cortex containing apparently normal neurons (*n*) and neuropile is separated from the implant by a narrow zone of astrocytosis (*A*). Alumina ceramic (196 days), polyethylene (196 days), and Teflon FEP C20 (92 days). $\times 400$

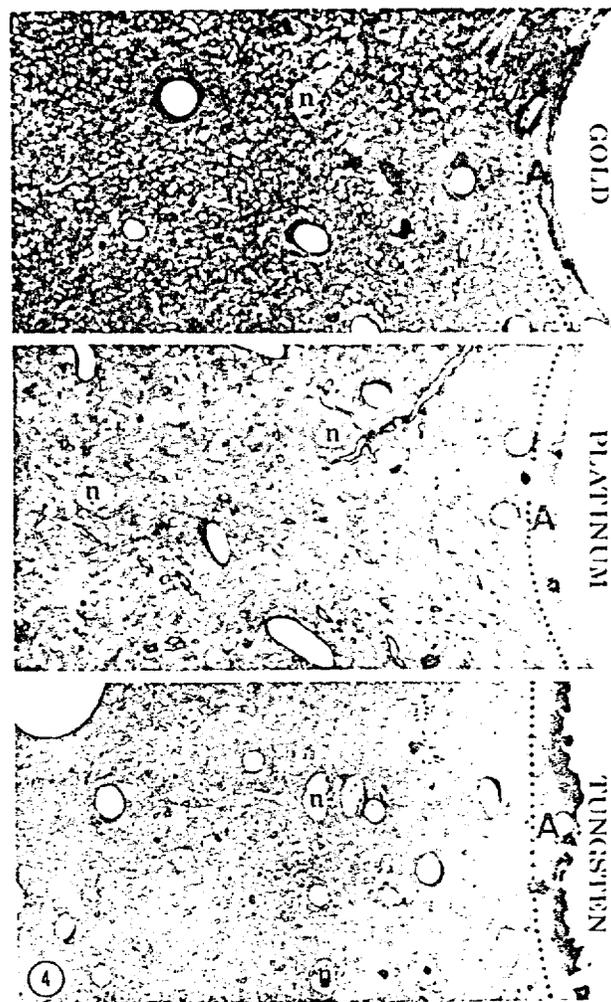


Fig. 4. Brain-implant boundary of non-reactive metal implants. The dotted line separates apparently normal cerebral cortex with neurons (*n*) from a narrow zone of astrocytosis (*A*). Gold (134 days), platinum (196 days), and tungsten (190 days). $\times 400$

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ples of other materials and could be correlated with the characteristics of neuropile in semithin sections examined by light microscopy.

The brain-implant boundary of the three non-reactive, non-metallic implants shown in Figure 3 was surrounded by cortical neuropile with a normal texture. Unstained profiles of dendrites extended to within a few micrometers of the implant, and nerve and glial cells of the gray matter appeared to be normal. The narrow zone of astrocyte processes at the implant surface resembled the zona limitans at the pial surface of the cerebral cortex. The non-reactive metallic implants illustrated in Figure 4 showed a similar pattern. However, the reactive metal implants shown in Figure 5 were surrounded by a thin layer of boundary cells and an abnormally wide zone of

astrocytic processes. Apparently normal neuropile, neurons, and glial cells extended to within 50 μm of the implant, and a small quantity of collagen was visible between the boundary cells and the cortical surface in electron micrographs of the boundary.

Moderately toxic implants were surrounded by a concentric zone of connective tissue with distinctive cellular constituents (see Fig. 6). Electron microscopy revealed that the dark, multinucleate giant cells apposed to the implant's surface contained numerous lysosomal dense bodies, were apposed to one another by numerous microvillar projections, and rested on a layer of collagen. Hypertrophic astrocytes were commonly observed in the zone of astrocytosis that forms the new cortical surface. The texture of neuropile in the adjacent gray matter was altered and often

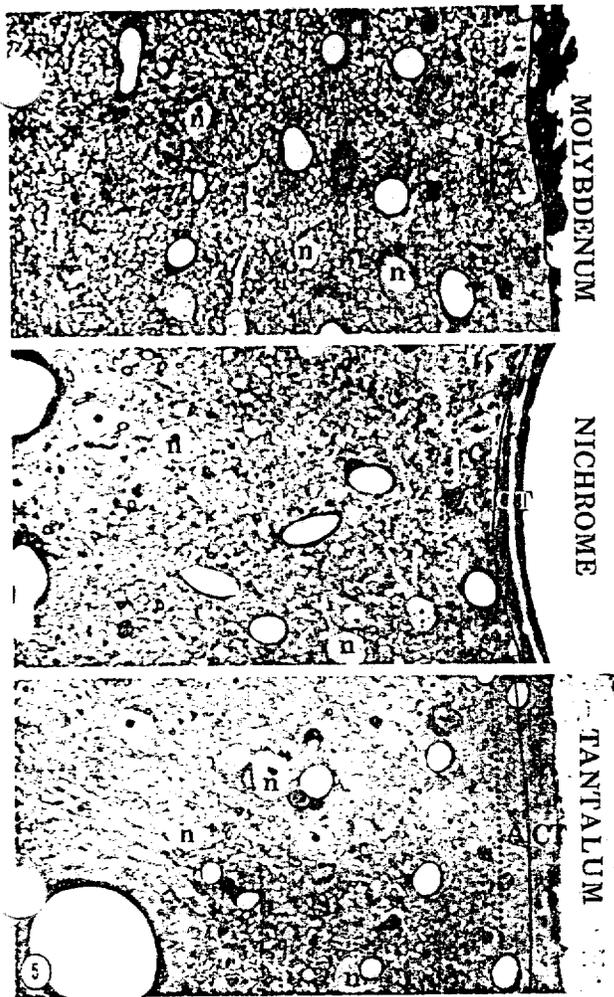


Fig. 5. The brain-implant boundary of reactive metal implants is marked by astrocytosis (A) and connective tissue (CT). Cerebral cortex with neurons (n) surrounds the zone of astrocytosis. Molybdenum (227 days), nichrome (197 days), and tantalum (196 days). $\times 400$.

displayed fewer light dendritic profiles than normal. Perivascular cuffing was typical of some but not all moderately toxic implants; as shown in Figure 6, cuffing occurred in the vicinity of silver, silastic RTV and germanium. The plasma cells and macrophages of the cuff were similar to cells found in the zone of connective tissue and sometimes contained reactive dense bodies that resembled the material at the implant surface.

Increasingly wider zones of connective tissue and astrocytosis were observed around the more toxic materials, iron and copper (Fig. 7A and B), and contained areas of presumed calcification. Semithin and ultrathin sections could be cut only after dilute hydrochloric acid had been applied to the block's surface.

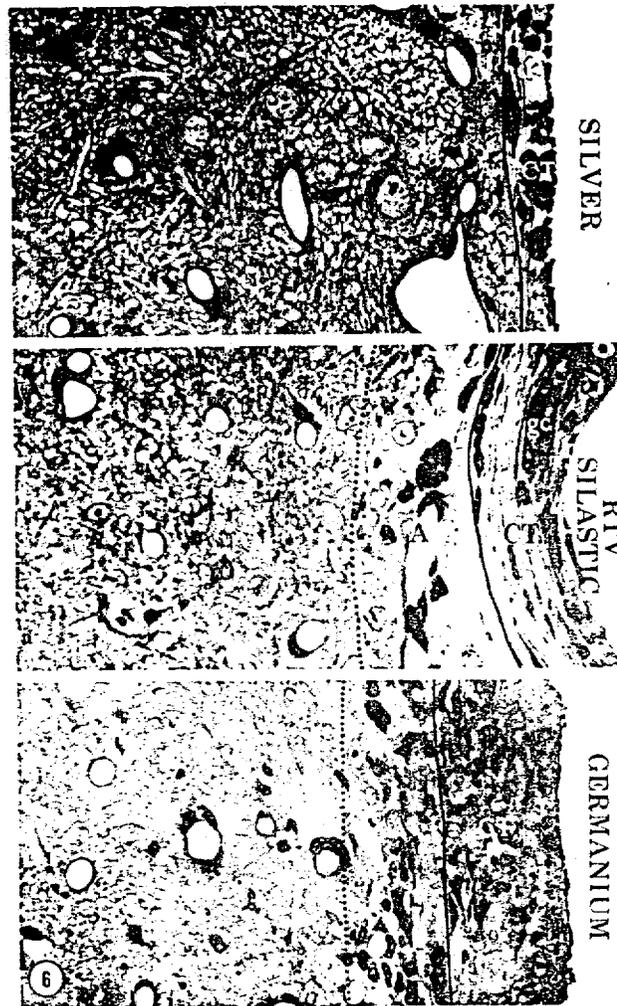


Fig. 6. The brain-implant boundary of moderately toxic implants is marked by a zone of astrocytosis (A) and connective tissue (CT) containing giant cells (gc). Altered cerebral cortex with perivascular cuffing and an increased number of small dark cells surrounds the zone of astrocytosis. Silver (175 days), silastic RTV (188 days), and germanium (220 days). $\times 400$.

Cobalt, the most toxic material tested, was separated from the gray matter by a wide, complex zone of astrocytosis. This finding corroborated that of Fischer (1968). Patches of dark, needle-like material were observed in the outer, lightly staining portion of this zone (see Fig. 7C), which was continuous with wide areas along the boundary of connective tissue that presumably contained extracellular deposits of calcium (see Fig. 8). Since the two areas had similar staining properties and looked similar under the electron microscope, we assumed that the material in the outer zone also probably represented some form of calcium. Concentric layers or subdivisions were consistent features of the connective tissue surrounding the central acellular necrotic core, and well-defined

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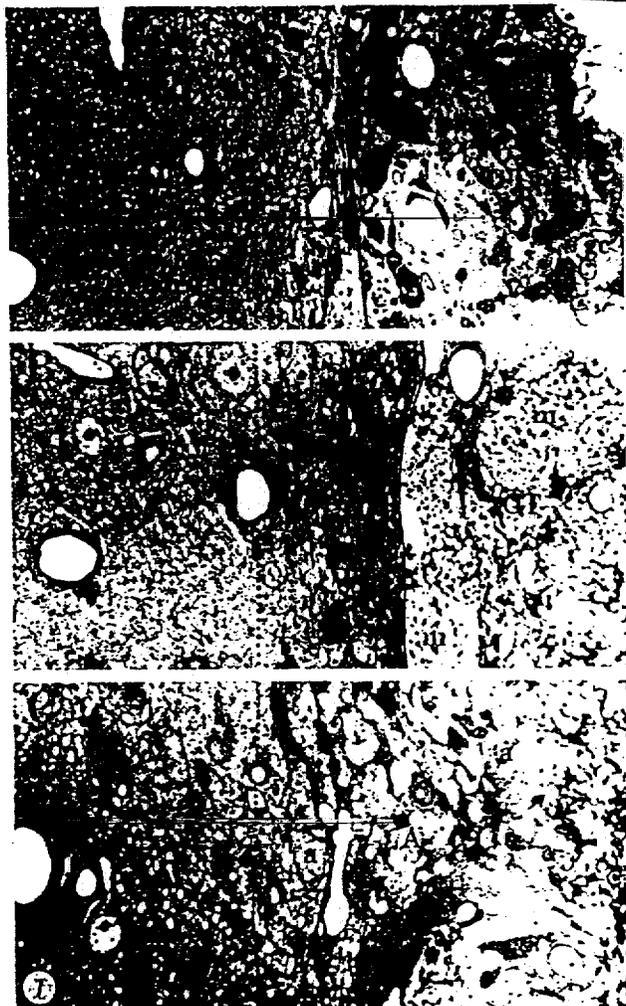


Fig. 7. The complex boundary surrounding toxic implants: iron (A), copper (B), and cobalt (C). Altered cerebral cortex surrounds the zone of astrocytosis (A). Macrophages (m) and giant cells (gc) are situated in the zone of connective tissue (CT) near iron and copper implants. Calcium (ca) and hypertrophic astrocytes (a) occur in the zone of astrocytosis near the cobalt implant. Iron (188 days), copper (192 days), and cobalt (270 days). $\times 400$



Fig. 8. Cobalt implant at low magnification illustrating the concentric zones of reactive tissue. Note the complex border (arrows) between the connective tissue and the zone of astrocytosis (A). Although macrophages and areas of calcification (ca) predominate in the zone of connective tissue, hypertrophic astrocytes (a) are also common. Neurons (n) occur near the zone of astrocytosis. The zone of necrosis adjacent to the implant is not shown because of the extensive width of the zone of connective tissue. (270 days.) $\times 200$

areas of giant cells and macrophages always occurred in the same relation to the implant.

Discussion

Precise histopathological determinations of the compatibility or toxicity of materials implanted in the brain are contingent upon the following: 1. the brain-implant boundary must remain intact, 2. the cellular constituents along the boundary must be identifiable, and 3. the observed changes must be distinguishable from those caused by mechanical trauma.

Detection of changes that occur near non-reactive or reactive materials depends on observations of the

actual brain-implant boundary. Thus, loss of portions of the boundary adhering to the implant during its removal from the brain for frozen or paraffin histological procedures prevents the examination of precisely that tissue which is most important for detailed histological analysis. We avoided this problem by leaving the implant in place during all stages of tissue preparation and by cutting plastic sections that included the brain-implant boundary. Because semithin sections allow a greater degree of optical resolution than do frozen or paraffin section, it was possible to identify subtle changes in the neuropile. Furthermore, the features observed with light microscopy were directly comparable to those observed with

on microscopy. Coordinated use of semithin ultrathin sections from the same block of material thus allowed positive identification of all reactive cellular and subcellular constituents and eliminated the need for the selective heavy-metal stains traditionally used for neuropathological analysis.

Variability in the characteristics of the boundary surrounding a given implant was typical of the pattern of response to all implanted materials. This was apparently the result of mechanical disruption of nervous tissue during implantation and differential movement of the brain with respect to the implant. We ruled out these changes by evaluating the reactivity or biocompatibility of each material on the basis of *minimal* histological changes at more than one level in individual specimens and by analyzing sections from several implants of the same material.

Non-Reactive and Reactive Implants

The brain-implant boundary of non-reactive implants was composed of a thin layer of astrocyte processes similar to the glia-limitans that normally forms the pial surface of the brain. In the absence of inflammation or trauma, there was intimate apposition between the implant and cortex with normal-appearing synapses within 5 μm of the implant. Implants surrounded by a high incidence of apparently normal gray matter indicated that displacement of tissue during its surgical introduction left the neuropile and vasculature intact. Nerve and glial elements thus withstand direct apposition to non-reactive material for long periods in the absence of ongoing mechanical trauma. That central nervous tissue can tolerate direct contact with a foreign body with virtually no reactive cellular changes confirms the findings of an earlier study (Stensaas and Stensaas, 1976), based on the analysis of a single type of epoxy plastic (Araldite).

Reactive materials showed varying degrees of biocompatibility. Although the boundary conditions were similar to those of non-reactive implants, more extensive change was indicated by the consistent presence of boundary or giant cells. These giant cells were similar to the epithelioid cells surrounding foreign bodies in the brain (Schultz and Willey, 1976) and in other tissue (Black and Epstein, 1974; Papadimitriou et al., 1973; Sutton and Weiss, 1966). The tendency of such cells to form a sheet and to be united by numerous small interdigitating processes suggests the possibility that these cells may impede the free exchange of material when interposed along the surface of the implant. However, cerebrospinal fluid layer of collagen interposed between boundary cells and astrocytes of the cortex also may permit attenuation of the noxious effects of the various

reactive materials. The cytological characteristics of boundary cells with prominent lysosomal constituents suggests a third possibility: namely, that these cells modify the effects of noxious agents arising from the implant by the uptake of material. An analytical electron microscopic investigation of the degree to which boundary cells engage in endocytosis and intracellular breakdown of material from the implant is now in progress.

Toxic Implants

Although our results indicate that central nervous tissue is vulnerable to the toxic effects of metals such as copper, iron, and cobalt, the character of reactive changes over long-term exposure to noxious agents suggests a common response pattern. The development of a capsule results from the concomitant development of meningeal connective tissue and gliosis. The extent of encapsulation presumably depends on local levels of toxicity. Whereas relatively modest zones of connective tissue are interposed between cortical gray matter and implants of substances such as copper, a complex capsule with calcification forms around extremely toxic materials such as cobalt. Other reports of mineralized tissue in the central nervous system (Mascherpa and Valentino, 1959; Bignami and Appicciutoli, 1964) indicate that mineralization is a consequence of changes which occur in extracellular fluid. Deposition of hydroxyapatite in metal-induced calcification probably occurs by the binding of cations with phosphate. According to Gabbiani et al. (1970), "the formation of apatite may constitute an effective means of fixing a potentially toxic compound". However, iron and other cations can react in vivo with collagen and may modify the structure of collagen so that it favors the precipitation of apatite. In the current study, we observed crystalline material not only in the extracellular space but in macrophages, astrocytes, and fibroblasts. Chou and Fukuhara (1973) saw membrane-bound "calcospherites" in glial cells following chronic methyl mercury poisoning. Thus, when evaluating an implant's toxicity, the presence of mineralization in the extracellular space or in macrophages, astrocytes, or fibroblasts should be investigated.

The connective tissue components of the capsule probably reduce local levels of toxicity by titration or spatial buffering. Thus the distance required for substances to reach the brain by diffusion through the interposed layer of connective tissue and cerebrospinal fluid would attenuate their effects. Continual turnover of fluid within the subarachnoid space may also serve to reduce the concentration of toxic by-products. A second, and qualitatively distinct

line of defense is provided by the complex feltwork of reactive astrocytes that forms around toxic implants. Although these astrocytes are intrinsically less capable of withstanding toxic products than are giant cells and meningeal elements, they are far better suited than neurons to tolerate these effects. The extensive necrosis of neuropile after implantation may be the primary stimulus for the reactive changes of astrocytes. Accordingly, the death of neuronal constituents would be followed by proliferation of the glial elements and better able to withstand changes produced by the implant (Cavanagh, 1970).

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S. S. Stensaas and L. J. Stensaas: Cortical Implants

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Received July 26, 1977 / Accepted September 24, 1977

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DBAC-17904A

Supply and Use Patterns for the Platinum-Group Metals



National Materials Advisory Board

Commission on Sociotechnical Systems

NMAB-359

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U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

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The platinum alloys commonly used for jewelry are Pt-10%Ir, known as "hard platinum" in the trade, Pt-5%Ru, and, in Europe, Pt-4%Pd, Pd-5%Ru is used as an all-precious metal, white gold. These alloys are used in cast and wrought form and for maximum prestige, reliability, and gem-retention in jewelry items. Rhodium, as a thin electrodeposit, is often used over these or silver jewelry to provide added whiteness, wear resistance, and immunity to tarnishing. A variety of platinum-group, metals-containing inks and pastes are used for the decoration of china, glass, and ceramics.

It might be well to make the point that because the jewelry application uses platinum preferentially, it frees large quantities of the other PGMs that might not otherwise reach the marketplace. Large quantities of rhodium, iridium, palladium, and ruthenium have been made available as the result of mining platinum to satisfy Japanese platinum jewelry demands. Severe and prolonged shortages of these metals would have occurred, and key industrial applications for them would have been halted or not exploited had these minor metals not been brought to the market.

5.5.7 Dental and Medical Uses

Platinum, palladium, and a variety of complex gold-silver-copper alloys that contain these elements find wide use as dental restorative materials (American Society for Metals, 1961b). Applications include dental crowns and caps produced by investment casting; bridges and orthodontic braces fabricated from wrought wire and strip; and a variety of pin, screw, plate, hinge, and strip devices used in dental and bone prosthetic treatments. For certain types of dental restorations, such as porcelain jacket crowns and porcelain bridgework, platinum or platinum-iridium alloys are preferred because they permit the use of superior porcelains of better appearance. In other less critical instances, the high cost of platinum has led to the enhanced use of the palladium-containing alloys. With the exception of orthodontic devices, these applications represent generally nonrecoverable uses of platinum-group metals.

The primary medical use of platinum-group metals in humans today is in cancer chemotherapy (National Academy of Sciences, 1977; Rosenberg, 1978). They are administered in the form of inorganic coordination complexes; one widely

investigated compound, cis-dichlorodiammine platinum (II), appears to be effective in the treatment of several important cancers. Other medical uses include the Pt-10Ir alloy in catheters for heart pacemakers and other body implant probes and electrodes, and Pt-30Ir for other special probes and hypodermic needle tubing.

5.5.8 Past and Current U.S. Usage Trends

The most significant event affecting the consumption of platinum-group metals in the United States has been their adoption as catalysts for the control of automotive exhaust emissions. In 1977 this represented our largest use for platinum (45 percent), a substantial use for palladium (18 percent), and an emerging use for rhodium (2 percent) in three-way catalysts. Trends affecting the consumption of platinum-group metals for the chemical and petroleum industries include the adoption of platinum-iridium catalysts for petroleum reforming and rhodium catalysts for acetic acid manufacture. Recent decreases in platinum sales reflect both increased efficiency in reforming catalysts and excess capacity in the chemical industry. Discerning trends in the chemical, petroleum, and glass industry is made more difficult both by their large inventories of platinum-group metals and their purchases in anticipation of future large installations.

In the electrical industry, the decreased use of palladium in contacts has already been noted, but the other significant trend is related to the use of ruthenium in dimensionally stable anodes and in thick-film resistors. Sales of ruthenium to this industry peaked in 1974 at the level of 44,000 troy ounces similar to an earlier peaking in chemical sales (approximately 40,000 troy ounces in 1972 to 1973) which may have reflected these same end uses.

A recent innovation in dental restoration technology is the use of porcelain veneering, and because of its wide adoption, palladium is emerging as the major precious metal for this use, replacing gold. This is due to the lower cost and greater strength of palladium alloys. Palladium is also replacing platinum and platinum-iridium alloys in dental restorations for similar reasons.

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TABLE 42 Dental and Medical Applications
(troy ounces annually)

<u>Platinum</u>			
<u>1977</u>	<u>1979-1983</u>	<u>1984-1988</u>	<u>Beyond 1988</u>
27,000	34,000	39,000	45,000

Comments:

This category is dominated by the dental field but includes significant quantities for use in alloys for heart pacemakers, catheters, etc. and as cis-platinum II for use in cancer chemotherapy in the medical field. The growth comes principally from the medical applications.

<u>Palladium</u>			
<u>1977</u>	<u>1979-1983</u>	<u>1984-1988</u>	<u>Beyond 1988</u>
112,000	125,000	157,000	250,000

Comments:

The field of prosthetic dentistry is the major consumer of palladium in this category

<u>Ruthenium, Iridium, and Rhodium</u>			
<u>1977</u>	<u>1979-1983</u>	<u>1984-1988</u>	<u>Beyond 1988</u>

(Estimated to be less than 2,000 troy ounces over the entire period.)

Comments:

These metals are used as alloying components with platinum and palladium. The total requirement is probably less than 2,000 ounces at maximum during the forecast period.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
1390 Piccard Drive
Rockville, Maryland 20850

JULY 11, 1990

COOK, INC.
ATTN: APRIL LAVENDER
925 SOUTH CURRY PIKE
P.O. BOX 489
BLOOMINGTON, IN 47402

D.C. Number : K901337
Product : HILAL EMBOLIZATION
MICROCOIL(TM)

Extended Until: 09/11/90

-- Based on your recent request, an extension of time has been granted for you to submit the additional information we requested.

If the additional information is not received by the "Extended Until" date shown above your premarket notification will be considered withdrawn.

If you have procedural or policy questions, please contact the Division of Small Manufacturers Assistance at (301) 443-6597 or their toll-free number (800) 638-2041, or contact me at (301) 427-1190.

Sincerely yours,

Robert I. Chissler
Premarket Notification Coordinator
Office of Device Evaluation
Center for Devices and
Radiological Health

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11

925 South Curry Pike P.O. Box 489
Bloomington, IN 47402 U.S.A.
Phone: 812 339-2235
Telex: 6711161 COOK UW
Telefax: 812 339-5369

COOK[®]

Cook Group Incorporated

July 3, 1990

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
1390 Piccard Drive
Rockville, MD 20850

FDA/CDRH/ODE/DMC

5 JUL 90 11 39

RECEIVED

DEVICE: Hilal Embolization Microcoil[™]
D.C.#: [REDACTED]

Dear Sir or Madam:

COOK INCORPORATED has received your request for additional information on the 510(k) notification of intent to market the above device.

To answer your questions concerning the 510(k) notification, additional data collection is required. For this reason, we would like to request a 60 day extension on the above referenced application.

Please let us know if an extension on our response period is approved. We can be reached by phone at 800-346-2686.

Thank you for your consideration.

Sincerely,

COOK INCORPORATED



April Lavender
Manager, Regulatory
Affairs

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
1390 Piccard Drive
Rockville, Maryland 20850

JUNE 11, 1990

COOK, INC.
ATTN: APRIL LAVENDER
925 SOUTH CURRY PIKE
P.O. BOX 489
BLOOMINGTON, IN 47402

D.C. Number : K901337
Product : HILAL EMBOLIZATION
MICROCOIL(TM)

Extended Until: 07/11/90

-- Based on your recent request, an extension of time has been granted for you to submit the additional information we requested.

If the additional information is not received by the "Extended Until" date shown above your premarket notification will be considered withdrawn.

If you have procedural or policy questions, please contact the Division of Small Manufacturers Assistance at (301) 443-6597 or their toll-free number (800) 638-2041, or contact me at (301) 427-1190.

Sincerely yours,

Robert I. Chissler
Premarket Notification Coordinator
Office of Device Evaluation
Center for Devices and
Radiological Health

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COOK[®]
Cook Incorporated

May 30, 1990

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
1390 Piccard Drive
Rockville, MD 20850

FDA-CDRH-ODE

MAY 31 1990

DOCUMENT MAIL CENTER

DEVICE: HILAL EMBOLIZATION MICROCOIL™
D.C.#: K901337

Dear Sir or Madam:

COOK INCORPORATED has received your request for additional information on the 510(k) notification of intent to market the above device.

To answer your questions concerning the 510(k) notification, additional data collection is required. For this reason, we would like to request a 30 day extension on the above referenced application.

Please let us know if an extension on our response period is approved. We can be reached by phone at 800-346-2686.

Thank you for your consideration.

Sincerely,

COOK INCORPORATED

April Lavender
April Lavender
Manager, Regulatory
Affairs

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

APR 30 1990

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

Ms. April Lavender
Manager, Regulatory Affairs
Cook Incorporated
925 South Curry Pike
P.O. Box 489
Bloomington, Indiana 47402

Re: K901337
Hilal Embolization Microcoil™
Dated: March 19, 1990
Received: March 22, 1990

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Dear Ms. Lavender:

We have reviewed your Section 510(k) notification of intent to market the device referenced above. We cannot determine if the device is substantially equivalent to a device marketed prior to May 28, 1976, the enactment date of the Medical Device Amendments, based solely on the information you provided. In order for us to complete the review of your submission, we require the following information:

(b)(4) Trade Secret Process- Product Specs



(b)(4) Trade Secret Process- Product Specs



We believe that this information is necessary for us to determine whether or not this device is substantially equivalent to a pre-Amendments device with regard to its safety and effectiveness.

You may not market this device until 90 days after you have provided adequate information described above and required by 21 CFR 807.87(f) and (h). If you market the device without conforming to these requirements, you will be in violation of the Federal Food, Drug, and Cosmetic Act (act). You may, however, distribute this device for investigational purposes to obtain any clinical data that is needed to establish substantial equivalence. Clinical investigations of this device must be conducted in accordance with the investigational device exemption (IDE) regulations.

If the requested information is not received within 30 days, we will consider your premarket notification to be withdrawn and your submission will be deleted from our system. If you submit the requested information after 30 days it will be considered and processed as a new 510(k); therefore, all information previously submitted must be re-submitted so that your new 510(k) is complete.

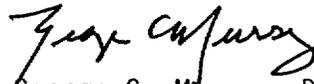
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Page 3 - Ms. April Lavender

If you have any questions concerning the contents of this letter, please contact Mr. A. Doyle Gantt at (301) 427-1053. If you need information or assistance concerning the IDE regulations, please contact the Division of Small Manufacturers Assistance at their toll free number (800) 638-2041 or at (301) 443-6597.

Sincerely yours,



George C. Murray, Ph.D.
Director
Division of Anesthesiology, Neurology,
and Radiology Devices
Office of Device Evaluation
Center for Devices
and Radiological Health

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DO NOT REMOVE THIS ROUTE SLIP!!!!

K-90-1337

4/30/90

FROM: COOK, INC. ATTN: APRIL LAVENDER 925 SOUTH CURRY PIKE P.O. BOX 489 BLOOMINGTON, IN 47402		LETTER DATE 03/19/90	LOGIN DATE 03/22/90	DUE DATE 06/20/90
SHORT NAME: COOK		TYPE OF DOCUMENT: 510 (k)		CONTROL # K901337
		ESTABLISHMENT NO: 1820334		
TO: ODE/DMC	CONT. CONF.: ? STATUS : H REV PANEL : NE PAN/PROD CODE(S): NE/ / /			
SUBJECT: HILAL EMBOLIZATION MICROCOIL(TM)				
DECISION: DECISION DATE: / /	RQST INFO	DATE: 04/30/90	INFO DUE DATE: 05/30/90	
		DATE: / /	DATE: / /	
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

APR 30 1990

Ms. April Lavender
Manager, Regulatory Affairs
Cook Incorporated
925 South Curry Pike
P.O. Box 489
Bloomington, Indiana 47402

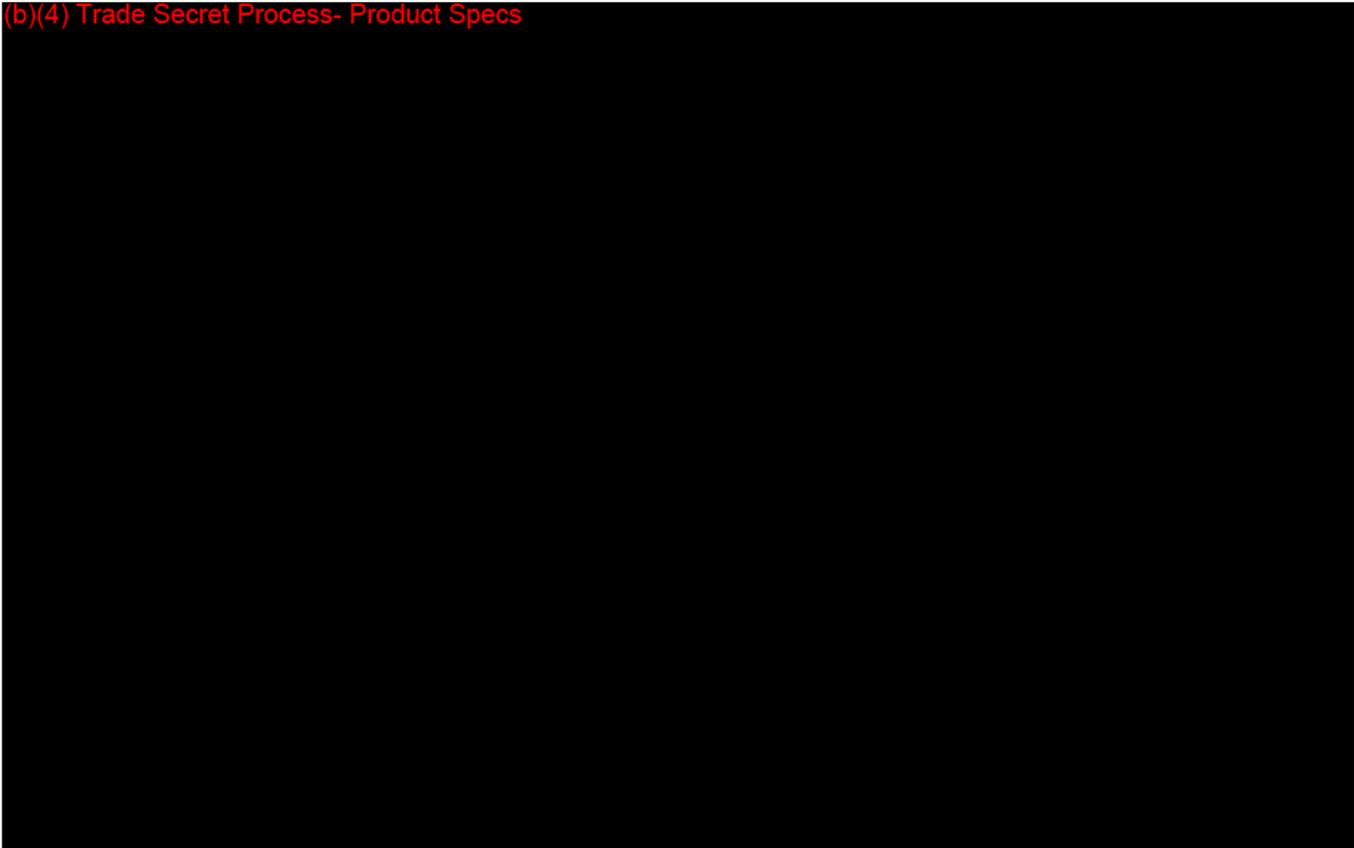
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Re: K901337
Hilal Embolization Microcoil™
Dated: March 19, 1990
Received: March 22, 1990

Dear Ms. Lavender:

We have reviewed your Section 510(k) notification of intent to market the device referenced above. We cannot determine if the device is substantially equivalent to a device marketed prior to May 28, 1976, the enactment date of the Medical Device Amendments, based solely on the information you provided. In order for us to complete the review of your submission, we require the following information:

(b)(4) Trade Secret Process- Product Specs

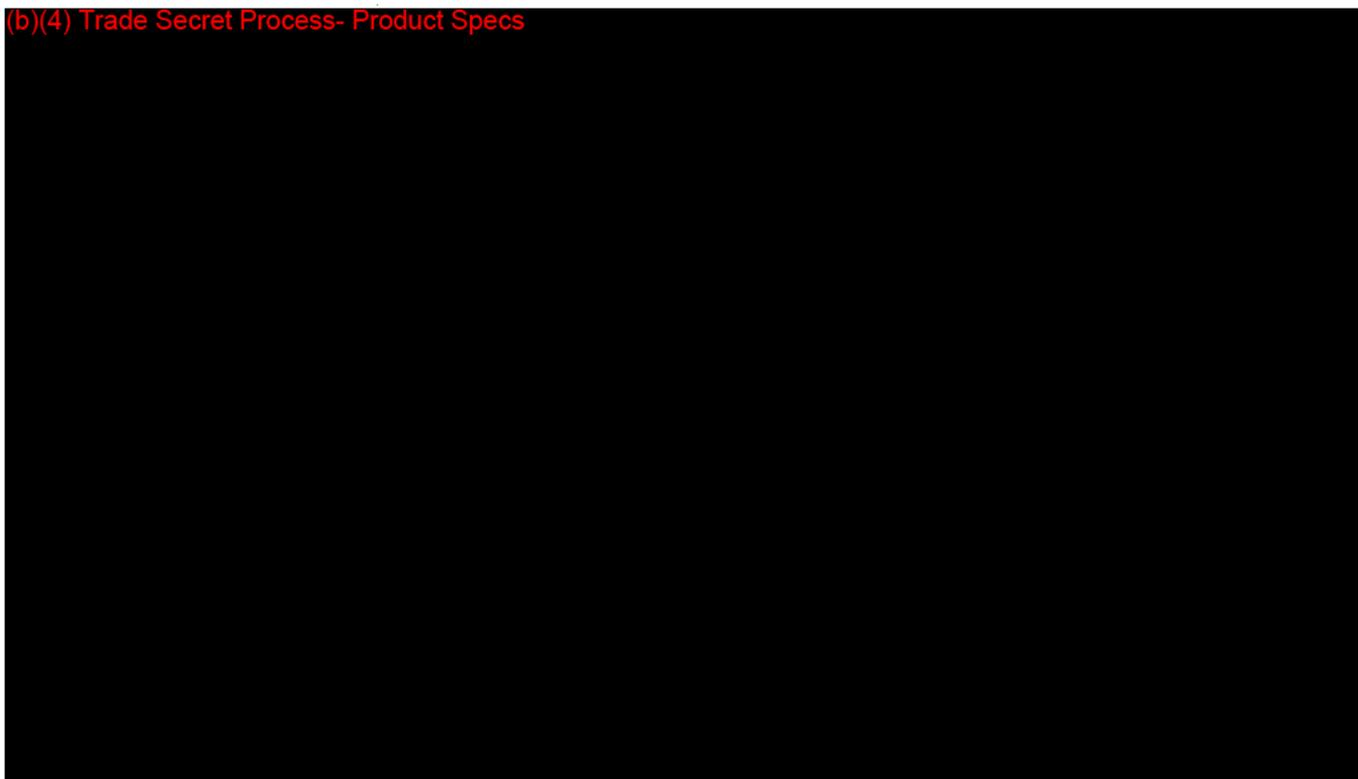


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OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HF2430	Crump	4/25/90						
HF2430	Munson	4/26/90						
2440	W. Brown	4/27						

85

(b)(4) Trade Secret Process- Product Specs



We believe that this information is necessary for us to determine whether or not this device is substantially equivalent to a pre-Amendments device with regard to its safety and effectiveness.

You may not market this device until 90 days after you have provided adequate information described above and required by 21 CFR 807.87(f) and (h). If you market the device without conforming to these requirements, you will be in violation of the Federal Food, Drug, and Cosmetic Act (act). You may, however, distribute this device for investigational purposes to obtain any clinical data that is needed to establish substantial equivalence. Clinical investigations of this device must be conducted in accordance with the investigational device exemption (IDE) regulations.

If the requested information is not received within 30 days, we will consider your premarket notification to be withdrawn and your submission will be deleted from our system. If you submit the requested information after 30 days it will be considered and processed as a new 510(k); therefore, all information previously submitted must be re-submitted so that your new 510(k) is complete.

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Page 3 - Ms. April Lavender

If you have any questions concerning the contents of this letter, please contact Mr. A. Doyle Gantt at (301) 427-1053. If you need information or assistance concerning the IDE regulations, please contact the Division of Small Manufacturers Assistance at their toll free number (800) 638-2041 or at (301) 443-6597.

Sincerely yours,

George C. Murray, Ph.D.
Director
Division of Anesthesiology, Neurology,
and Radiology Devices
Office of Device Evaluation
Center for Devices
and Radiological Health

cc: HFZ-401 DMC
HFZ-402 RChissler
HFZ-430 DANRD

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Memorandum

4/25/90

REVIEWER(S) - NAME(S)

Gantt

Subject 510(k) NOTIFICATION

K901337

To THE RECORD

It is my recommendation that the subject 510(k) Notification:

- (A) Is substantially equivalent to marketed devices.
- (B) Requires premarket approval. NOT substantially equivalent to marketed devices.
- (C) Requires more data.
- (D) Other (e.g., exempt by regulation, not a device, duplicate, etc.)

Additional Comments:

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The submitter requests under 21 CFR §807.95:

Predicate Product Code w/Panel and class:

- No Confidentiality
- Confidentiality for 90 days
- Continued Confidentiality exceeding 90 days

Additional Product Code(s) w/Panel (optional):

REVIEW:

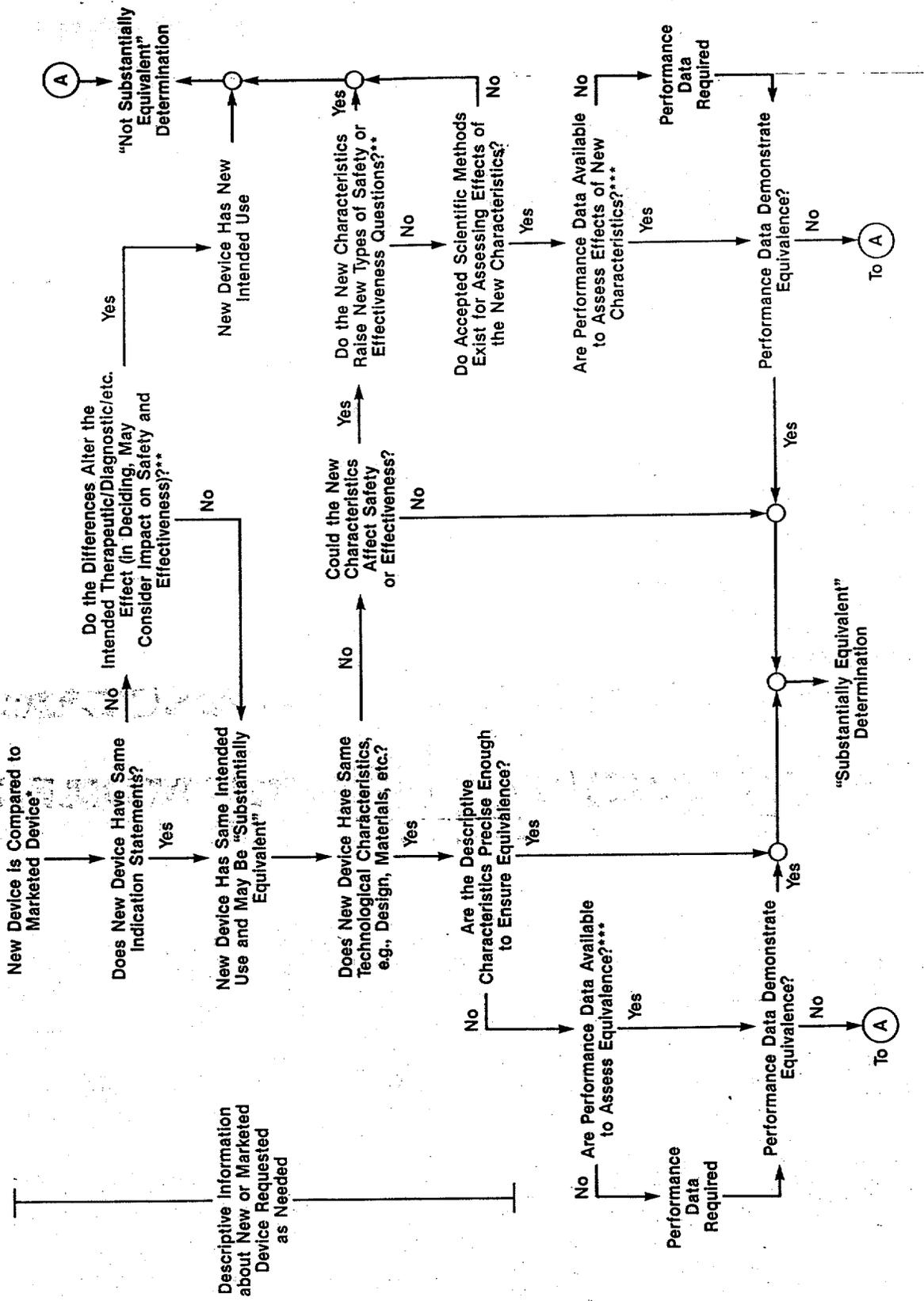
[Signature] *4/26/90*
(BRANCH CHIEF) (DATE)

FINAL REVIEW:

[Signature] *4/27/90*
(DIVISION DIRECTOR) (DATE)

K
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510(k) "Substantially Equivalent" Decision-Making Process (Detailed)



* 510(k) Submissions Compare New Devices to Marketed Devices. FDA Requests Additional Information if the Relationship Between Marketed and "Predicate" (Pre-Amendments or Reclassified Post-Amendments) Devices is Unclear.
 ** This Decision is Normally Based on Descriptive Information Alone, But Limited Testing Information is Sometimes Required.
 *** Data May Be in the 510(k), Other 510(k)s, The Center's Classification Files, or the Literature.

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Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
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1390 Piccard Drive
Rockville, Maryland 20850

MARCH 24, 1990

COOK, INC.
ATTN: APRIL LAVENDER
925 SOUTH CURRY PIKE
P.O. BOX 489
BLOOMINGTON, IN 47402

D.C. Number : K901337
Received : 03-22-90
90th Day : 06-20-90
Product : HILAL EMBOLIZATION
MICROCOIL(TM)

-- The Premarket Notification you have submitted as required under Section 510(k) of the Federal Food, Drug, and Cosmetic Act for the above referenced device has been received and assigned an unique document control number (D.C. Number above). Please cite this D.C. Number in any future correspondence that relates to this submission.

We will notify you when the processing of this submission has been completed or if any additional information is required. You are required to wait ninety (90) days after the received date shown above or until receipt of a "substantially equivalent" letter before placing the product into commercial distribution. We intend to complete our review expeditiously and within ninety days. Occasionally, however, a submitter will not receive a final decision or a request for additional information until after ninety days has elapsed. Be aware that FDA is able to continue the review of a submission beyond the ninety day period and might conclude that the device is not substantially equivalent. A "not substantially equivalent" device may not be in commercial distribution without an approved premarket approval application or reclassification of the device. We, therefore, recommend that you not market this device before FDA has made a final decision. Thus, if you have not received a decision within ninety days, it would be prudent to check with FDA to determine the status of your submission.

All correspondence concerning your submission MUST be sent to the Document Mail Center at the above address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification application. Telefax material will not be accepted nor considered as part of your official premarket notification application, unless specifically requested of you by an FDA official.

If you have procedural or policy questions, please contact the Division of Small Manufacturers Assistance at (301) 443-6597 or their toll-free number (800) 638-2041, or contact me at (301) 427-1190.

Sincerely yours,

Robert I. Chissler
Premarket Notification Coordinator
Office of Device Evaluation
Center for Devices and
Radiological Health

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901337

COOK®

Cook Incorporated

March 19, 1990

FDA-CDRH-ODE

MAR 22 1990

DOCUMENT MAIL CENTER

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
1390 Piccard Drive
Rockville, MD 20850

SUBJECT: 510(k) Premarket NotificationTM
DEVICE: Hilal Embolization MicrocoilTM

Dear Sir or Madam:

The purpose of this letter is to notify the Food and Drug Administration pursuant to Section 510(k) of the Federal Food, Drug and Cosmetic Act, that COOK INCORPORATED intends to market the Hilal Embolization MicrocoilTM.

The following information is submitted:

- Classification Name: Occlusion Device
Common/Usual Names: Occluding Spring Emboli
Trade/Proprietary Name: Hilal Embolization MicrocoilTM
- Establishment Registration Number: 1820334
- The FDA has classified embolization coil devices in Class III.
- No performance standards applicable to embolization coil devices have been established by the FDA.
- Draft labeling for the Hilal Embolization MicrocoilTM is enclosed as Exhibit I. The labeling of the device includes product information sheets, suggested instructions for use, package labeling and a sample of the device.

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6. The Hilal Embolization Microcoil TM is comparable to the COOK MWCE (Occluding Spring Embolus) and WCE (Gianturco) embolization coils. The following describes these comparable devices in terms of sample order number, manufacturer, and device name.

<u>Sample Order Number</u>	<u>Manufacturer</u>	<u>Name</u>
MWCE-38-4-3	COOK INCORPORATED	Occluding Spring Embolus
WCE-21-5.5-0	COOK INCORPORATED	Gianturco Coil

Refer to Exhibit II for labeling, product information sheets, suggested instructions for use and drawings for the curled MWCE and curled and straight WCE embolization coils.

7. See Sections A-H as enclosed for Device Description Data and further information on similar devices.
8. Please incorporate by Reference D.C.#K885124.

We consider our intent to market this device as confidential commercial information. We request that it be considered as such by the FDA and not available through Freedom of Information except where required by law. We have not disclosed our intent to market this device to anyone except employees of our establishment and have taken precautions to protect this confidentiality.

Please address technical concerns to Neal E. Fearnot, Ph.D., E.E. at 317-463-7537 and administrative concerns to the undersigned at 800-346-2686.

Sincerely,

COOK INCORPORATED



April Lavender
Manager, Regulatory
Affairs

Enclosures

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510(k) Premarket Notification
Hilal Embolization Microcoil™

DEVICE DESCRIPTION DATA

A. INTENDED USE

Hilal Embolization Microcoils™ are intended for use for embolization of selective vessel supply to arteriovenous malformations (AVMs) and other vascular lesions of the brain, spinal cord and spine.

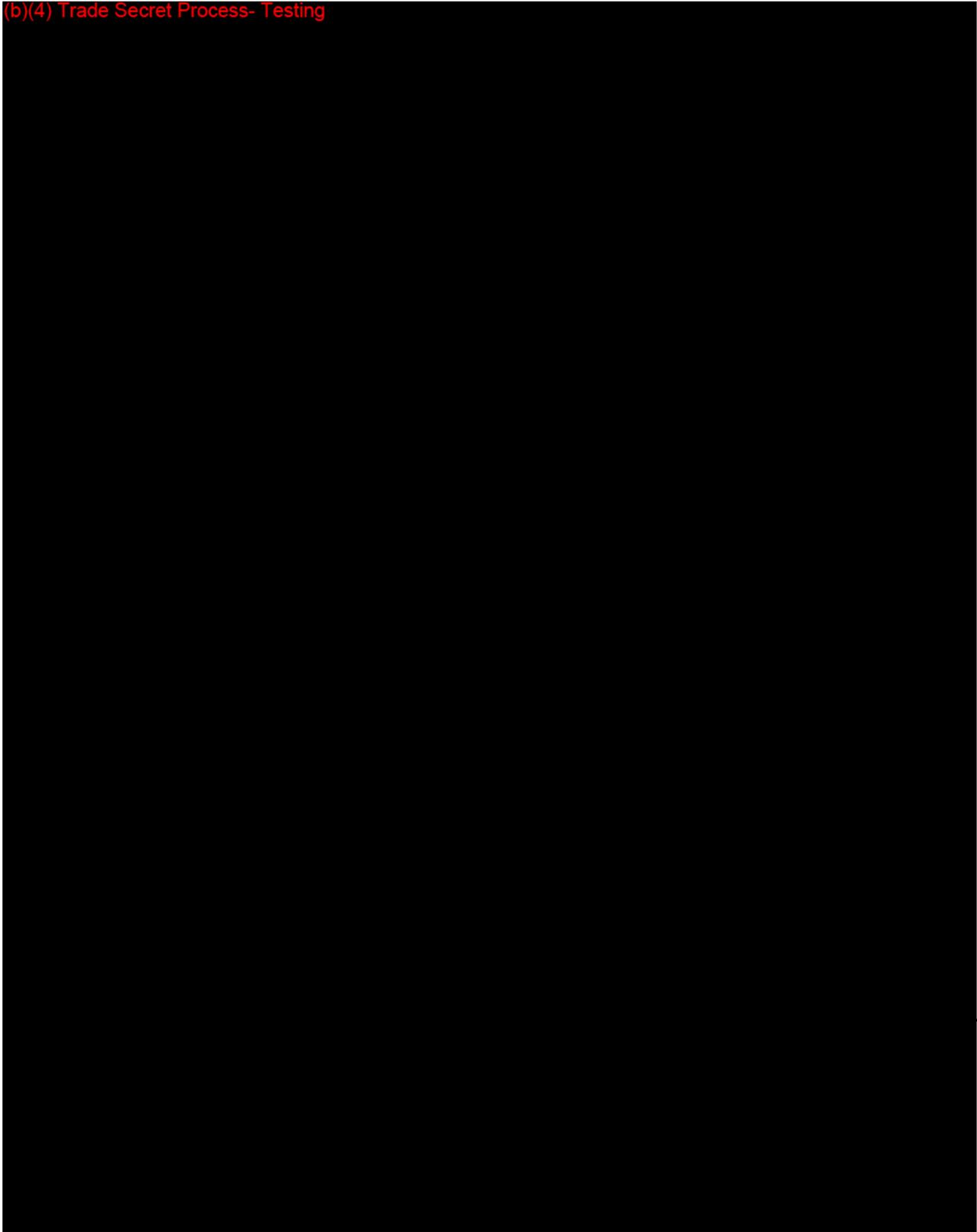
B. PHYSICAL COMPOSITION

B.1 Refer to figure 1 for pictorial representations of the device and to figure 2 for drawings of engineering specifications. (b) (4)

(b) (4)

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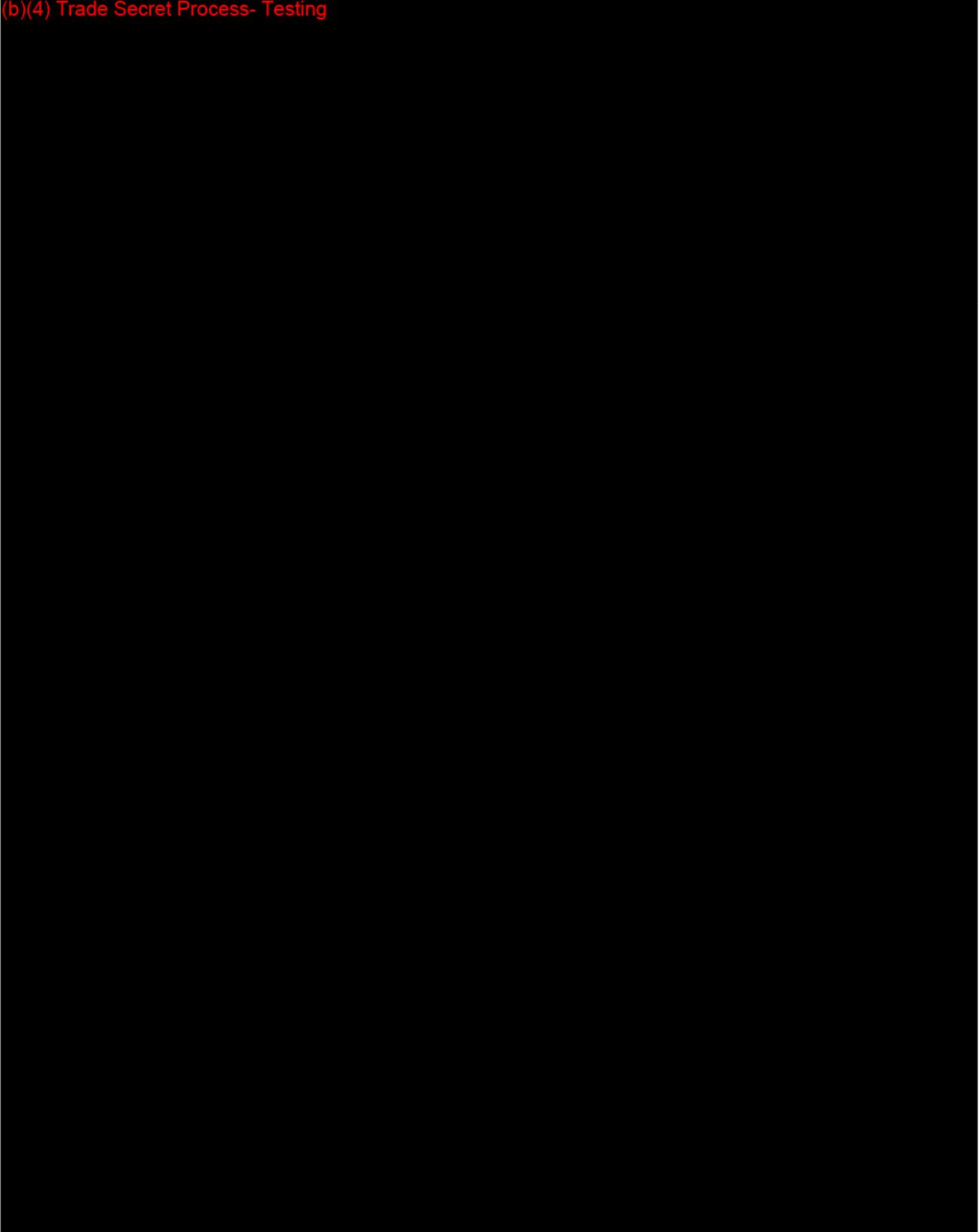
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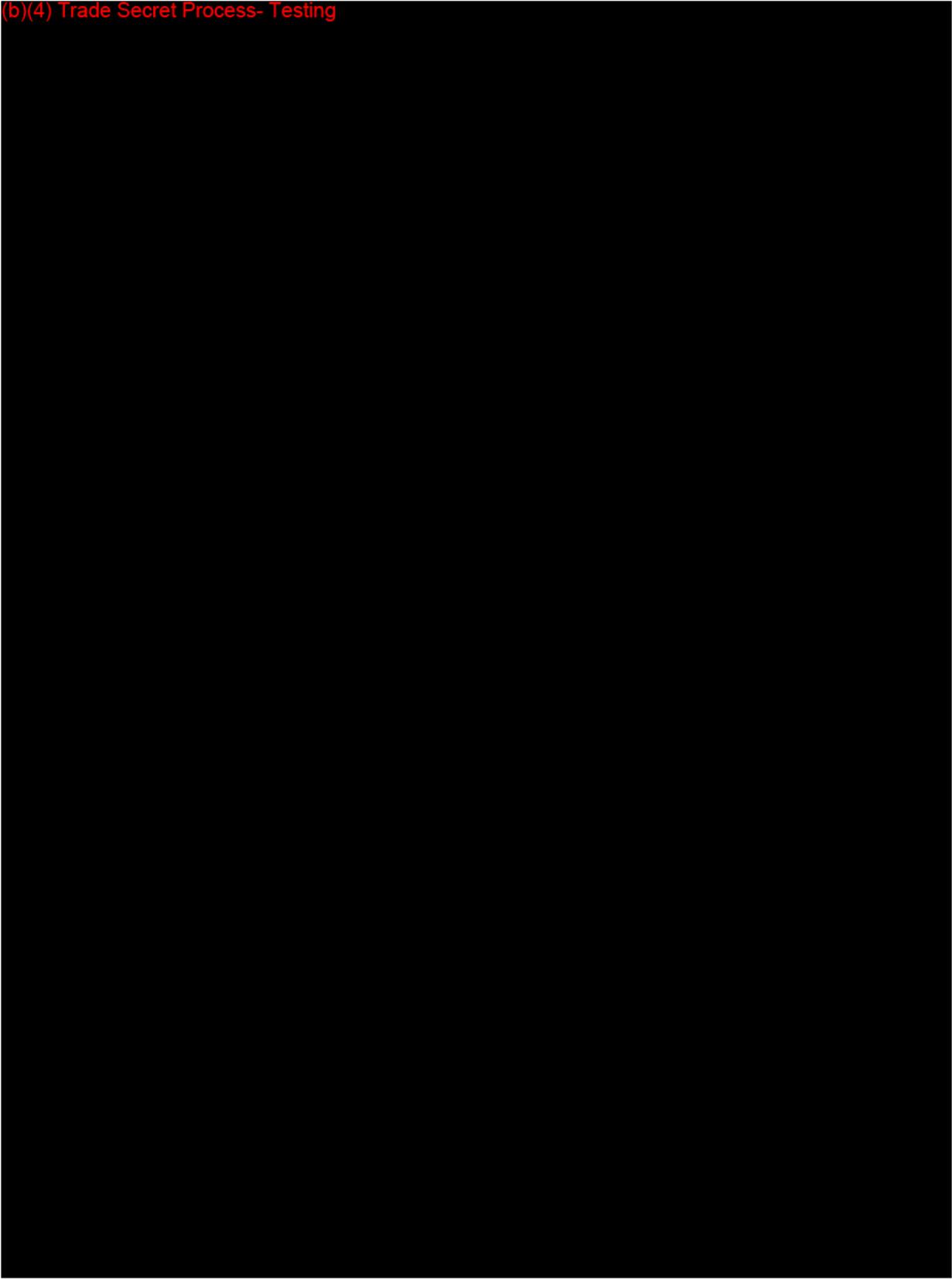
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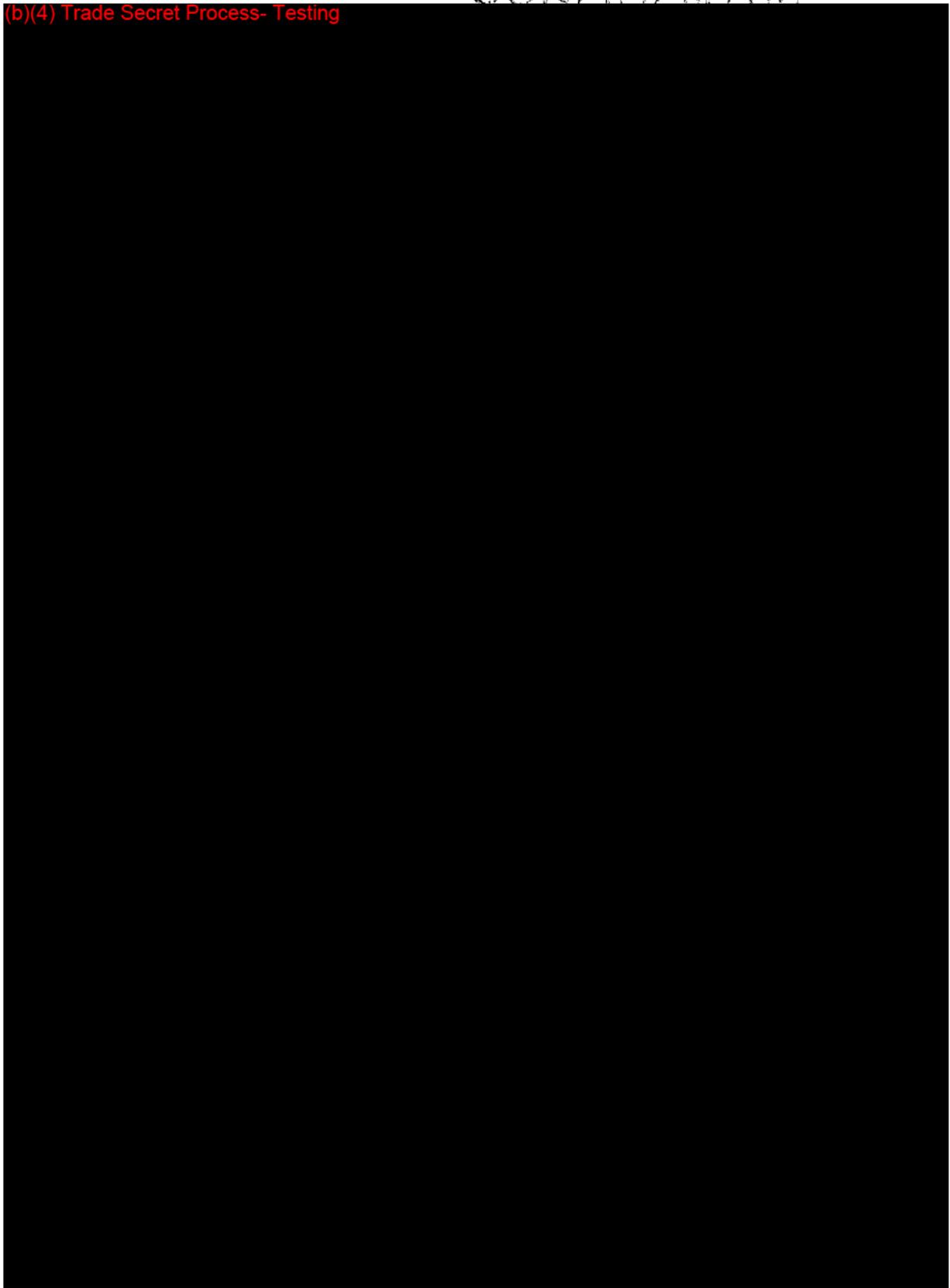


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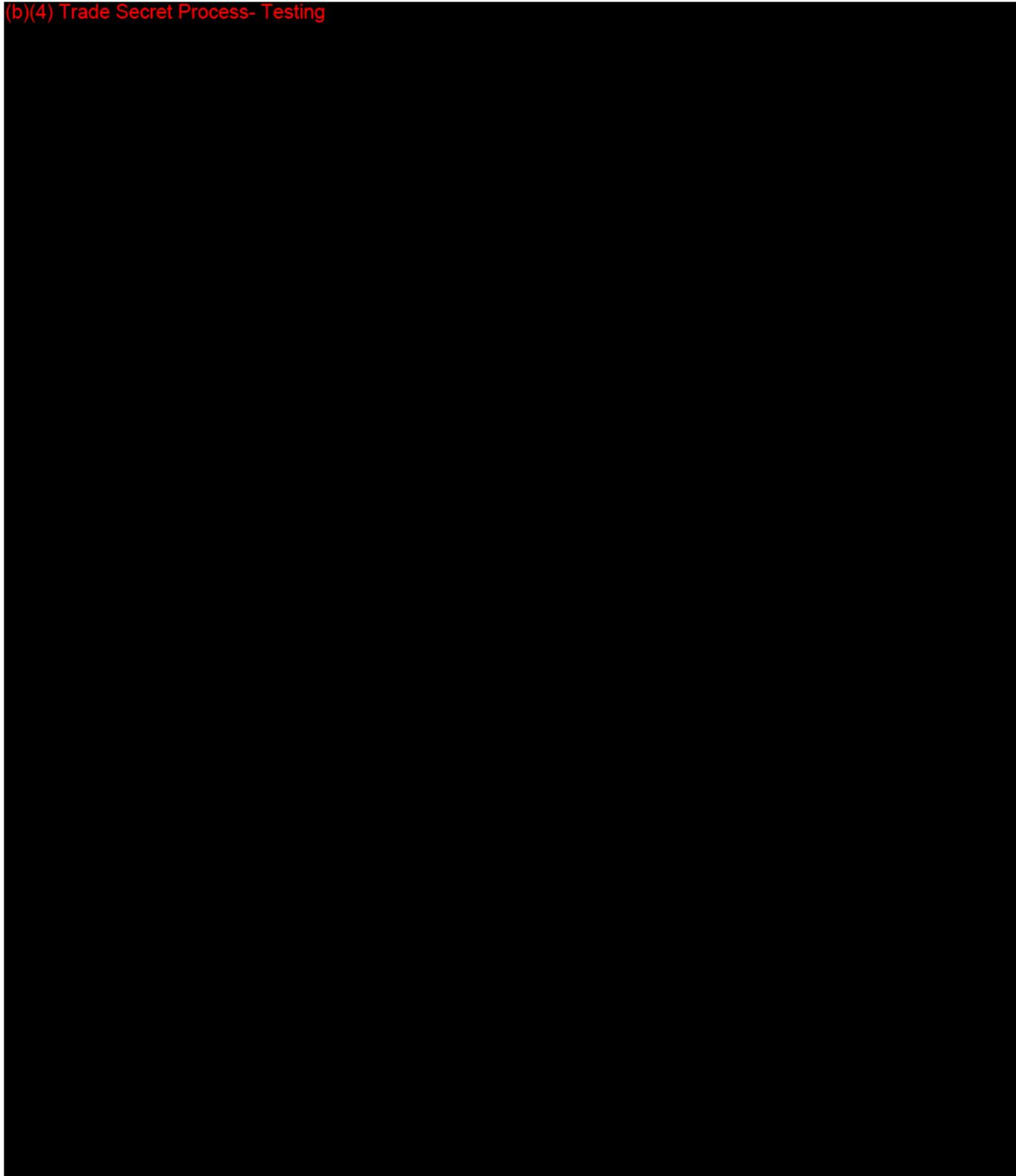
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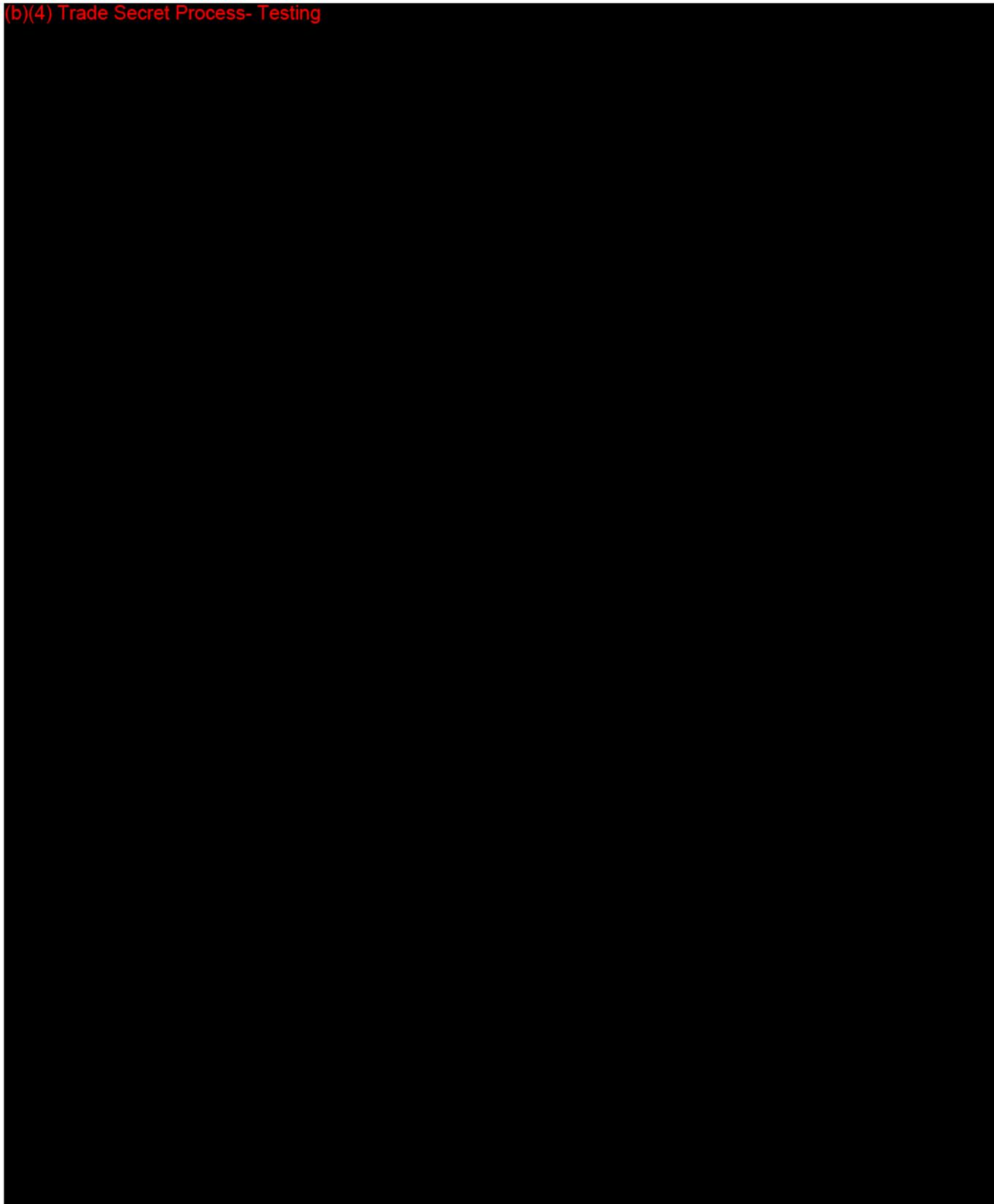
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C. METHOD OF OPERATION

The Hilal Embolization Microcoil™ is used for vascular embolization in a variety of vascular lesions affecting the brain, head and neck, spinal cord and spine. Use requires experience with intravascular catheterization with the capability of navigating to the third and fourth order branches of the intracranial arteries using high quality fluoroscopy.

The catheter should be placed with the tip near a vascular lesion or malformation. The microcoils are inserted in the catheter and advanced with a teflon-coated guide wire to the base of the skull. A straight microcoil travels the remaining intracranial course of the catheter by a small injection of saline delivered with a 1 or 3cc syringe. By this means, the microcoil is gently advanced under fluoroscopic control with the saline injection and is deposited near the tip of the placed catheter in the nidus of the vascular malformation. The curled microcoils are placed using standard wire guide pusher techniques. Each microcoil is inserted individually and its position verified by fluoroscopic control. Use of the microcoils allows incremental and gradual occlusion of a given vascular branch or area, allowing the operator to optimize the amount of occlusion. Another ability of microcoil use is to block a predetermined segment of an arterial feeder, allowing the operator to perform a safe and adequate resection.

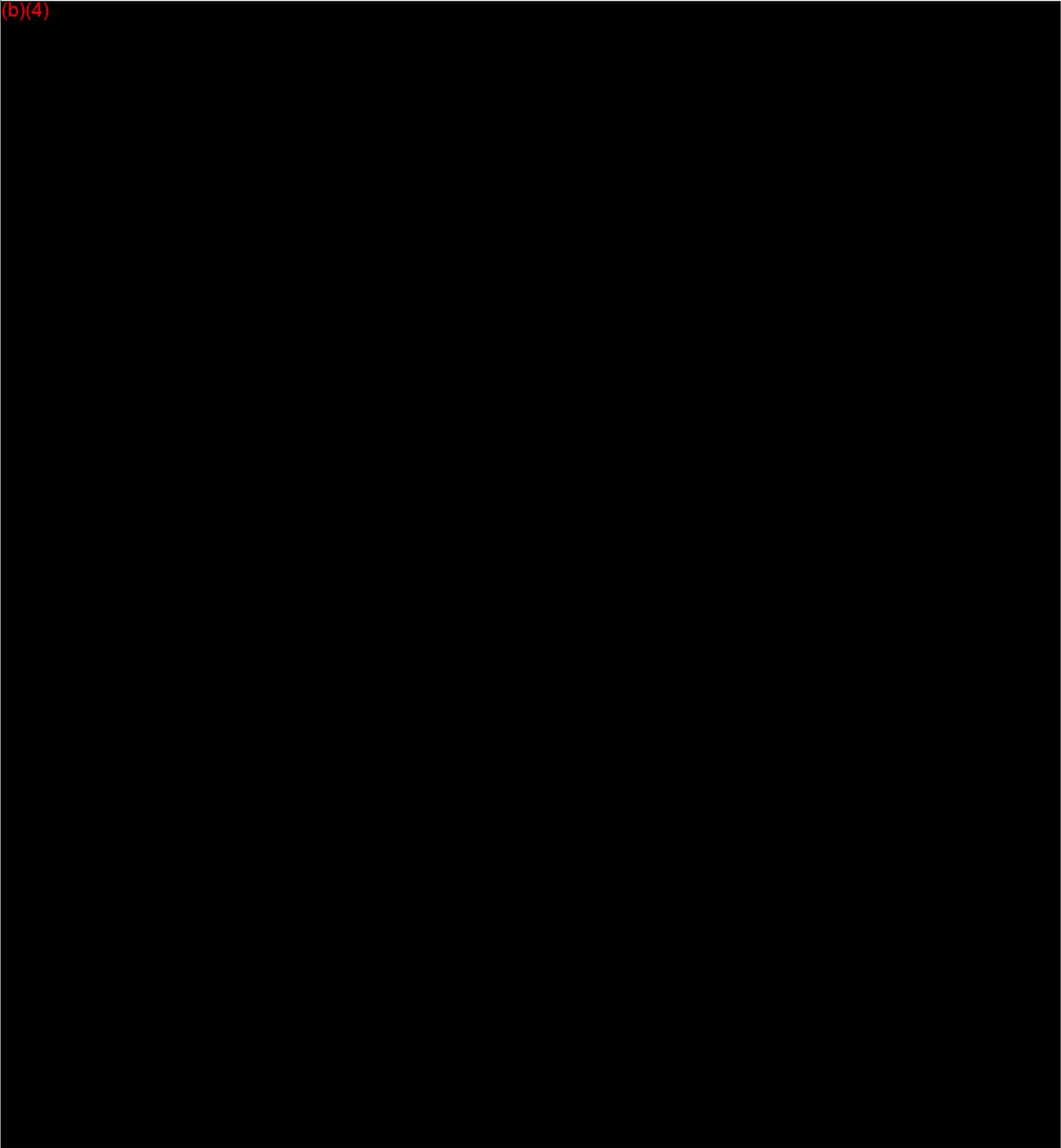
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D. SPECIFICATIONS

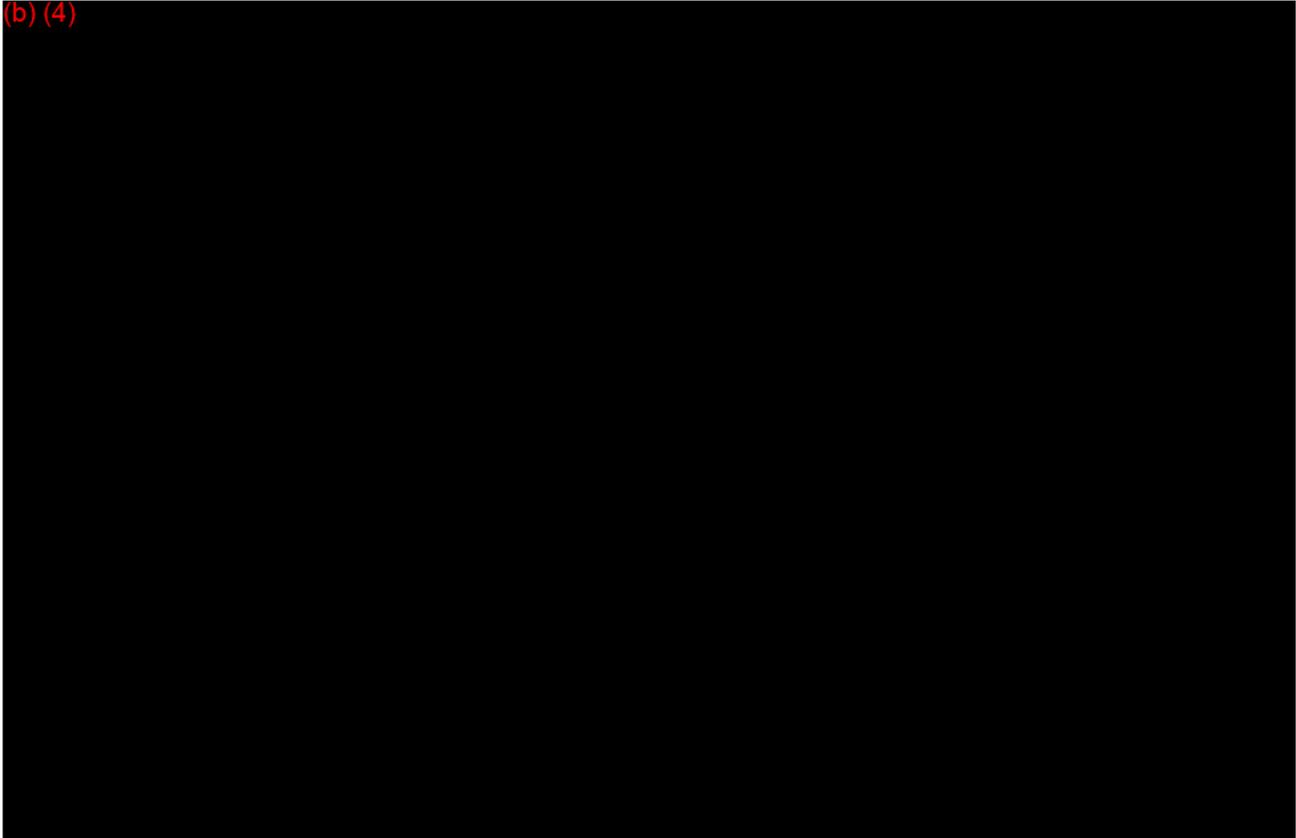
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(b) (4)



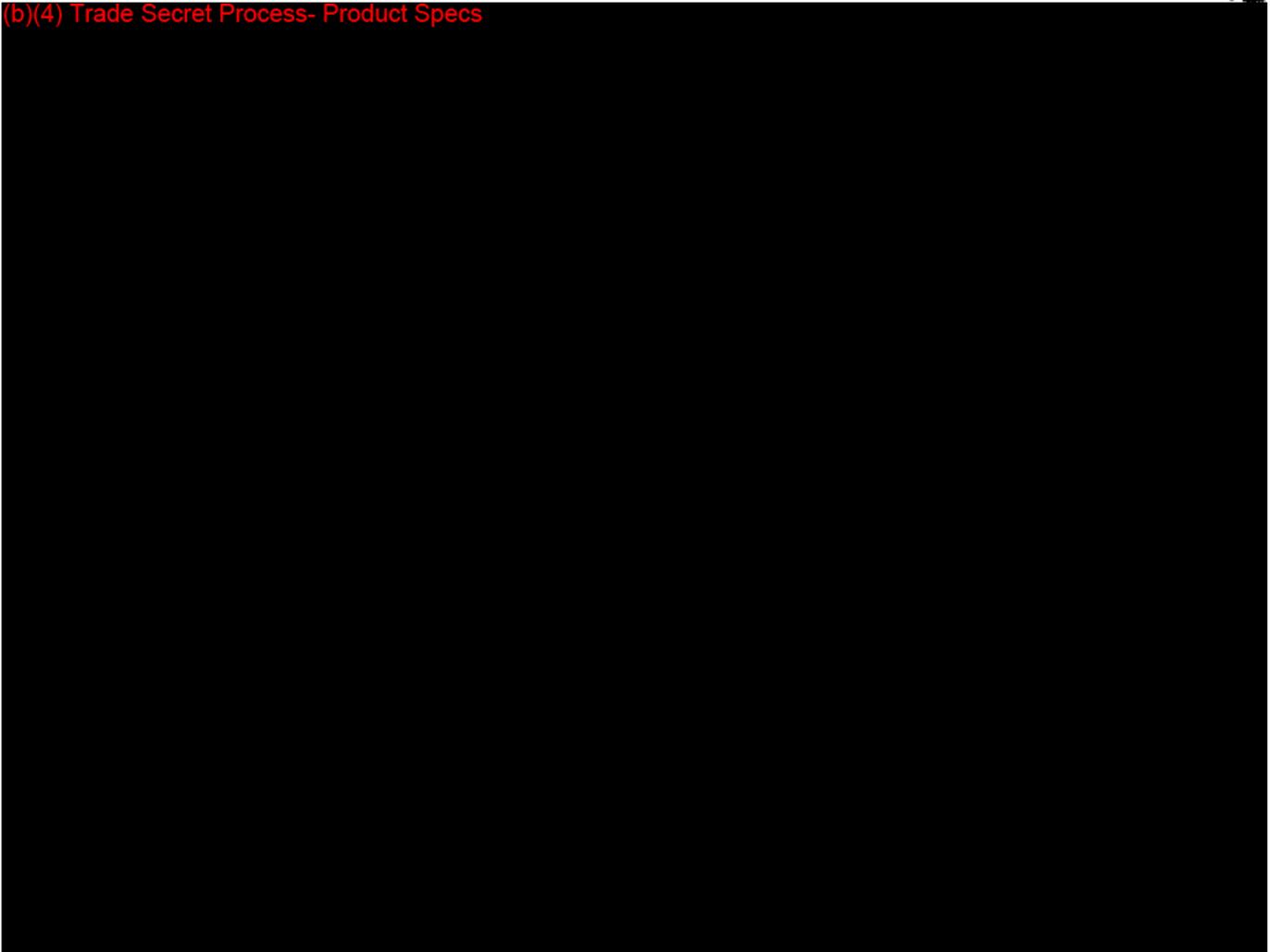
As indicated in the product information sheet, Hilal MicrocoilsTM are recommended for use with catheters whose inside lumen dimension does not exceed 0.027-inch and with wire guides measuring 0.018-inch outside diameter.

A typical order number for a COOK delivery catheter would be:

T3.OS	-	NT	-	100	-	P	-	NS	-	O
Teflon French Size		Endhole Non- Tapered		Length CM		Fitting Plastic		Number of Sideports		Tip Config- uration

Recommended wire guides should be Teflon coated with a flexible tapered distal tip. A typical order number for a COOK wire guide would be:

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F. PACKAGING INFORMATION

The Hilal Embolization Microcoils™ will be packaged for storage and shipment using polyester-polyethylene film/Tyvek. The package will be sealed, inspected and ETO sterilized prior to shipment.

G. STERILIZATION

(b)(4) Trade Secret Process- Product Specs



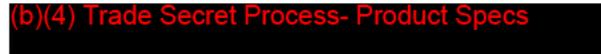
(b)(4) Trade Secret Process- Product Specs



H. COMPARABLE DEVICES

We believe this device is comparable to preamendment devices and qualifies for 510(k) approval. The Hilal Embolization Microcoils™ are similar to commercially available Cook MWCE embolization coils (Occluding Spring Embolus). These coils are manufactured by Cook Incorporated and were marketed prior to enactment of the Medical Device Legislation under the product family name of WCE coils or Gianturco stainless steel coils.

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(b)(4) Trade Secret Process- Product Specs

The Occluding Spring Embolus was designed for percutaneous insertion through either a tapered or non-tapered catheter for arterial and venous vessel embolization.

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(b)(4) Trade Secret Process- Product Specs

The curl

diameter is available in 3, 5 and 8mm

(b)(4) Trade Secret Process- Product Specs

(b)(4) Trade Secret Process- Product Specs

Packaging consists of polyester-

polyethylene film/Tyvek with ETO sterilization.

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The reordering information for the preamendment coil is described as follows:

Pre-1976 (design WCE) -- Examples of the order number for individual coils were:

Curled - WCE-35-5.7-3(5, 7, 10)

Straight - WCE-21-5.5-0

-- An example of the reorder number for the embolization coils with recommended delivery system was:

GAO-1
Superselektive Set

Current (design MWCE) -- Examples of the order number for the individual coils are:

- Curled - MWCE-38-5-3
- Straight - MWCE-38-5-0

The Hilal Embolization Microcoil™ is almost identical to the Occluding Spring Embolus. The Hilal Embolization Microcoil™ is also designed for percutaneous insertion through either a tapered or non-tapered catheter for arterial and venous vessel embolization.

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(b)(4) Trade Secret Process- Product Specs

Packaging consists

of polyester-polyethylene film/Tyvek with ETO sterilization.

(b)(4) Trade Secret Process- Product Specs

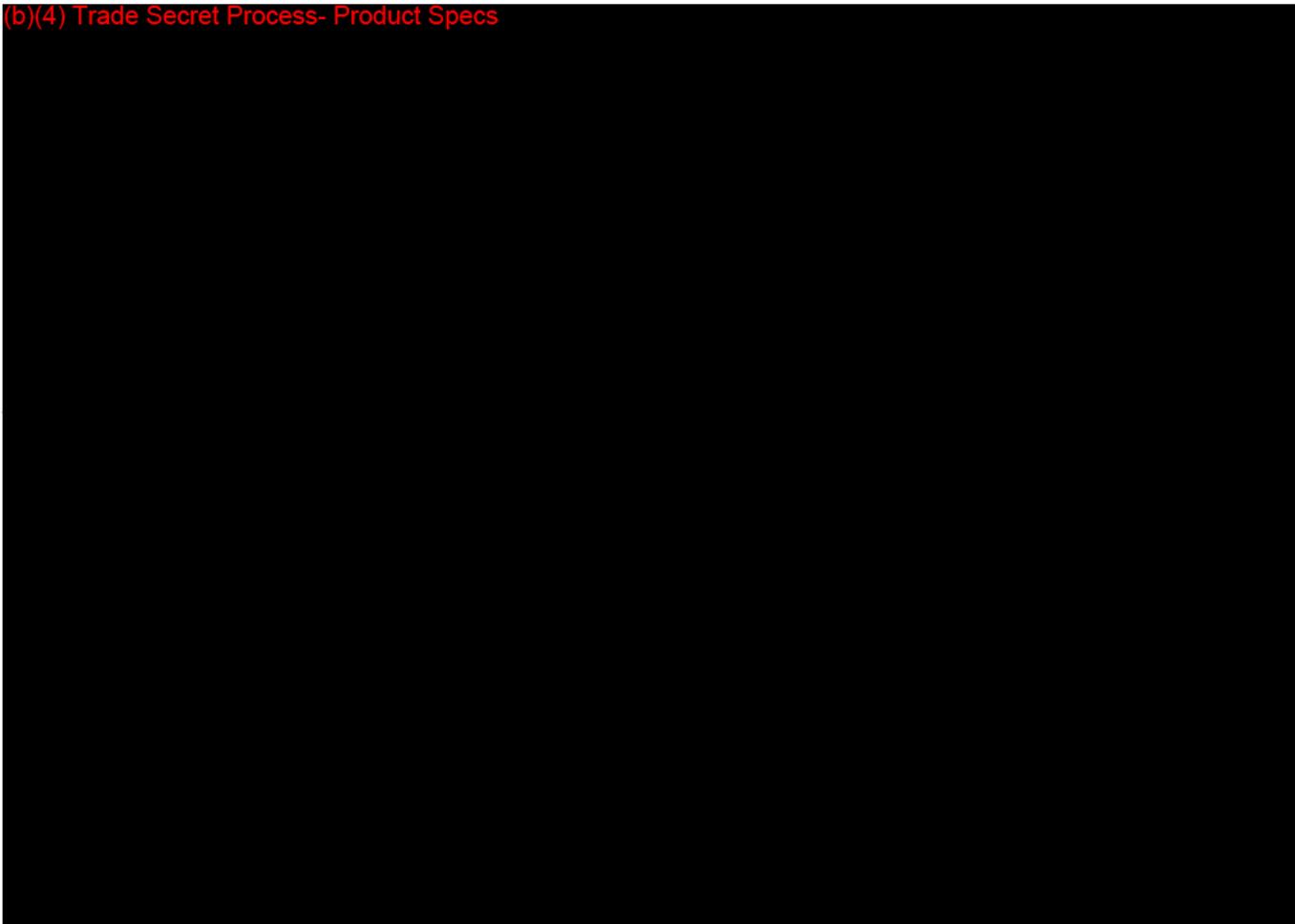
Another difference between the Occluding Spring Embolus and the Hilal Embolization Microcoil™ is the available configurations. The Hilal Embolization Microcoil™ is

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available in either a straight or curled configuration. The Occluding Spring Embolus, MWCE design, has been supplied in a curled configuration only. However, straight coils, WCE design, have been previously used, prior to the 1976 amendment. A drawing of the straight coil and a paper referencing its use, both originating prior to 1976, are shown in Exhibit VI.

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H.1 Literature Review

Transcatheter arterial embolization has been employed in the treatment of tumors and arteriovenous

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malformations (AVMs) of the central nervous system since the late 1960's. If AVMs can be obliterated by embolization, it is easier and safer to treat it by this means than by operative resection. When operation is impossible because of the site or morphology of the malformation or of the clinical state of the patient, embolization may offer an alternative mode of treatment. Embolization may entirely obliterate the malformation or at least reduce its volume. It should be noted that embolization does not preclude surgical intervention. In some vascular tumors, it can be considered as a preparatory step to operation, either to reducing the risk of hemorrhage by diminishing the blood flow or to eliminate certain inoperable or difficult afferent vessels.

H.1.1 Review of Therapeutic Embolization in Areas of the Brain, Spinal Cord and Spine

As reported by Djindjian et al. (1973), isolated embolization of an operable cerebral arterial venous malformations was pioneered by Luessenhop et al. (1962), who utilized silastic spheroids to embolize lesions via the extracranial carotid vessels. Luessenhop showed that the emboli usually follow the increased flow of blood supplying the malformation and that silastic beads may take up to 24 hours or even longer to reach their

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ultimate destination. In Djindjian's paper, the authors describe the technique, indications and complications of embolization in the external carotid and medullary territories based on 60 cases of vascular tumors and AVMs. The embolizations, using 1cm strips of gelfoam injected via a solution of physiological saline, were carried out by femoral approach with superselective catheterization of either branches of external carotid or intercostal arteries under television control. Following an injection of contrast medium, studies were made to localize the emboli accurately and to assess the extent of the arterial occlusion produced. They found that embolization of the feeding pedicles of an AVM sometimes causes dilatation of adjacent arteries which may also require embolization. External carotid AVMs that possess voluminous feeding arteries should not be embolized with gelfoam because they found complete occlusion impossible. In these cases, gelfoam, providing partial embolization, should be used in conjunction with larger silastic beads or surgical ligation to treat the malformation.

Kricheff et al. (1972) describes a transfemoral percutaneous catheterization technique for embolization of intracranial AVMs. The embolization

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material used was silastic spheroids, varying from 1-3mm in diameter. Attempts were made to use the smallest pellets possible so that they could lodge within the malformation rather than in feeding vessels. The radiopaque silastic pellets were placed in the orifice of the adaptor using small forceps or needle point and were gently flushed through the catheter by saline hand injection. Post-embolization reassessment of the flow through the AVM was by means of repeat angiography as well as by pre-and post-embolization isotopic flow studies. The authors felt that the radiologic catheter technique for embolization was superior to the direct arteriotomy approach since no surgical incision or general anesthesia was required. With no damage to the carotid or vertebral arteries, it was possible to perform repeated embolization at a later date, if necessary, without sacrifice of an artery or reoperation through a previously scarred site.

Wolpert and Stein (1975) combined the advantages of embolization and surgical resection in the treatment of a small number of large AVMs of the cerebral hemisphere. Eleven patients were treated by embolization from February 1974 to March 1975 with surgery following in eight patients. In

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all eleven cases, the size and location of the AVM was such that surgery without prior embolization was considered hazardous. Radiopaque barium impregnated silastic beads up to 2mm in diameter were introduced under fluoroscopic control and their passage into the AVM observed. The beads were introduced until either the AVM was obliterated, their circulation time through the AVM was significantly increased, there was a significant increase in the visualization of normal vessels to the adjacent normal brain, or normal vessels were occluded. All patients had pre- and post-embolization angiograms. Due to the development of collateral arterial supply to a partially treated AVM, these authors felt that surgical removal of the AVM should be carried out if at all possible. The opportune time for operation following successful embolization remains speculative. Their data suggest surgery be delayed following embolization since angiograms performed up to 24 days have shown a progressive decrease in the diameter of feeding arteries. A delay must be weighed against the adverse effect of the development of collateral channels and enlargement of previously small feeders to the AVM. Aberrant emboli to normal vessels were seen in a high percentage of their cases, an obvious drawback of

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using silastic beads. However, where AVMs were either large with voluminous blood flow or situated in such critical areas of the brain that surgery could not be considered feasible, the risks of embolization were considered to be less than the risks of eventual intracerebral hemorrhages and death. In conclusion, the authors felt that embolization aided significantly in the surgical resection of large AVMs. When embolization was feasible, they found they were able to perform operation with favorable results where previously they had not been able to consider any surgical procedure.

Ruggiero et al. (1976) reported on a glomus tumor treated by embolization of the vertebral artery. The large glomus tumor was supplied by the left internal and external carotid arteries and by the left vertebral artery. Emboli of spongostan were injected into the ascending pharyngeal artery which was selectively catheterized. The patient improved, but two months later he was readmitted to the hospital because his condition had worsened. Embolization was repeated by injecting emboli via the external and vertebral arteries of the left side. Except for a small part of the tumor supplied by a branch of the carotid siphon, the tumor

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disappeared. The patient improved very quickly and was still in good condition after one year.

Hilal and Michelsen (1975) reported on embolization techniques for extra-axial vascular lesions of the head, neck and spine. The goal was to occlude the feeding arterial branches as close as possible to the lesion and thereby reduce the opportunity for collateral supply. There were clinically favorable results in 21 of 27 patients. Of the 27 patients, 14 had embolization with silastic spheres only, 5 with gelfoam only, and 1 with a combination of gelfoam and spheres. The remaining 7 patients had embolization with silastic adhesives. In 11 of the 21 patients, the procedure was preoperative and caused a dramatic reduction of surgical blood loss. In 10 of the 21 patients, therapeutic embolization alone resulted in a significant, clinical amelioration documented by a detailed follow-up varying from 2 to 5 years. No clinical effect was observed in four cases and in two cases serious complications occurred including one death. Both complications were due to reflux of emboli in the internal carotid artery. There were no infections, vascular necrosis or other complications. These authors believe the use of gelfoam should be limited to presurgical

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embolization since there was a tendency for recanalization in a few days, gelfoam was difficult to see radiographically, and carried a higher risk of complications. Silastic spheres were more stable and easily seen, however the procedure lasted about 3 hours, required a large amount of fluid, and on occasion the spheres proved cosmetically unsightly if they lodged in the scalp vessel. These authors favored the use of liquid silastic adhesive as it was considerably faster and easier for the patient. They noted, however, that experience was limited with this method and more complete evaluation was required for further study.

The above referenced studies show the feasibility of embolization in the nervous system. In summary, early methods resulted in obliteration of the AVM or reduction in volume to aid in surgical resection. Embolizing agents included silastic beads, gelfoam and silastic adhesives, used separately or in combination. The method obviated the need for direct arteriotomy in many cases (Kricheff et al., 1972) and aided significantly in reducing the surgical resection risks (Wolpert and Stein, 1975). While radiopaque silastic beads or spheres were easily seen and provided stable embolization, occlusion was gradual and aberrant

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emboli to normal vessels were seen in a large number of cases (Wolpert and Stein, 1975). Gelfoam provided rapid clotting due to its thrombogenicity, but it was difficult to see radiographically and vessels sometimes recanalized within several days. Since large pieces of gelfoam can pass through small catheters, if reflux occurs, gelfoam had the potential for occluding larger vessels leading to a higher risk of complications. Silastic adhesives provided rapid occlusion, however precise placement was of utmost importance and since experience was limited, it was felt further evaluation was needed (Hilal and Michelsen, 1975).

While these studies show the feasibility of embolization in areas of the brain, spinal cord and spine, the following studies describe the use of microcoils as an embolization agent for the treatment of AVMs in other areas of the body.

H.1.2 Review of Embolization Using Microcoils

Gianturco et al. (1975) reported on the use of two types of mechanical occluding devices, one consisting of cotton tails attached to a segment of steel tubing for use in smaller arteries and the other consisting of woolen strands attached to a wire coil for use in larger vessels. The cotton

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tail embolus consisted of a 3mm segment of #19 gauge steel tubing to which 8 strands of 5mm long cotton threads were attached. Selective catheterization of branches of the coronary, renal, celiac and superior mesenteric arteries was accomplished in 10 anesthetized dogs. The cotton tails were impaled on the centrally tapered mandril of a #20 gauge needle and inserted into the catheter through the opened stopcock. The mandril and needle were withdrawn, leaving the embolus in place in the catheter. Saline was injected to push the cotton tail through the catheter into the artery where the embolus was transported by the blood stream and provided occlusion by lodging in a small artery or at a bifurcation, usually where the arterial diameter was 2mm or less. For the occlusion of larger arteries, early prototype wool coils were used. Four woolen strands, 3cm long, were attached to a tightly coiled 5cm long segment of steel guide wire from which the central core had been removed. Canine superior mesenteric, renal, hepatic, splenic, carotid and iliac arteries were selectively catheterized. The steel coils with woolen tails were straightened by an introducer to facilitate passage through the catheter and then deposited near the terminal curl of the catheter. The coil was

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then pushed into the arterial lumen with a modified 0.045" guide wire. To provide occlusion, the wool coil formed an embolus of steel and wool at a point immediately distal to the catheter tip. Reexamination two weeks after the procedure revealed persistent occlusion. These authors also reported on a clinical case using wool coils for preoperative occlusion of the renal artery in a patient with a hypernephroma. The left renal artery was selectively catheterized and four woolen coils were used to occlude the vessels supplying the majority of the neoplasm. As a result of the embolization, the operative procedure was much easier and the coils did not interfere with ligation of the renal artery. In summary, embolization was accomplished using cotton tails and wool coils in canine, coronary, celiac, superior mesenteric, renal, hepatic, splenic, carotid and iliac arteries. Successful embolization with wool coils was also accomplished for preoperative occlusion of the renal artery in a patient with hypernephroma (Gianturco et al., 1975).

In 1976, Goldstein et al. reported on the use of stainless steel coils with attached woolen strands for central and permanent occlusion of larger vessels. Coils were straightened and

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inserted into a selectively placed catheter. A guide wire was then used to push the coil out of the catheter and into the artery. The coil reformed and obstructed the vessel distal to the catheter tip. When permanent vascular occlusion was desirable, the authors found gelfoam to be suitable for embolization followed by stainless steel coils. Due to the thrombogenicity of gelfoam, more rapid clotting occurred and maximal obliteration of tumor vascularity was achieved with the additional use of steel coils.

Wallace et al. (1976) references use of the Gianturco stainless steel coil for permanent intravascular occlusion of the proximal portion of the renal hepatic and internal iliac vessels describing clinical experience in the therapeutic management of 24 patients. The Gianturco stainless steel coil occluding device was formed from a 2.5" segment of stainless steel guide wire from which the central core was removed. The guide wire segment was preshaped in the form of a helix, 3/16" diameter. Four 2" long wool strands were attached to the tip of the coil and served as a nidus for thrombosis. The coil with attached wool strands was straightened and placed in a cartridge and an introducer was used to pass the coil through the

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cartridge and into the catheter. The coil was deposited in the distal portion of the catheter by withdrawing the mandril from the introducer and then pushed out of the catheter into the vessel lumen by a guide wire where it resumed its spiral shape. The steel coil and wool strands tightly intertwined forming a plug immediately distal to the catheter tip causing complete obstruction. In approximately 10 minutes, clot formation on the metal and wool insured more complete vascular occlusion. The authors reported that in most cases usually two coils, but as many as five, were inserted in the vascular bed to accomplish the occlusion.

Taylor et al. (1978) reported on a case history of therapeutic embolization using microcoils for the treatment of a pulmonary arteriovenous fistula. The occluding devices each consisted of a 5cm segment of steel guide wire with 3cm wool tails. These devices were placed into the vessels feeding the fistula as an alternative to further surgery. Twenty minutes after placement of the last two coils, the fistula was almost totally occluded and no complications were noted.

Fuhrman et al. (1984) described embolization of congenital thoracic vascular anomalies in infants and children using Gianturco steel coils coated with

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Dacron strands. The coils were straightened over a thin wire and fed through the catheter lumen by a flexible guide wire emerging in the abnormal vessel as a loose coil of 3, 5 or 8mm diameter. The first coil was chosen so that extruded diameter exceeded the angiographically estimated vessel lumen by approximately 50%. After placement of the coils, occlusion occurred by thrombosis, generally within 10 minutes. If complete occlusion was not angiographically apparent 5 or 10 minutes after initial placement, smaller coils were lodged in the remaining vessel lumen to further obstruct the vessel. Fifteen of 17 vessels were successfully occluded. No complications or errors in placement of coils occurred. Four of five children clearly benefited from the procedure. One died in spite of partial occlusion. Fuhrman showed that coil embolization can be performed accurately and safely even in small infants with a high rate of successful occlusion and may prove to be a valuable adjunct to operable management.

Lois et al. (1988) reported on embolization of systemic to pulmonary collateral vessels and shunts in fifteen patients using Gianturco-Wallace stainless steel coils of various diameters. In some cases, a combination of polyvinyl alcohol foam

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particles, gelatin sponge particles soaked in absolute alcohol, vascular spiders or detachable balloons were used with the Gianturco-Wallace coils. Embolization of large vessels was usually carried out with a 5 French catheter using 0.038" coils of the appropriate diameter. Smaller vessels were occluded using 0.025" mini coils delivered through a 3 French coaxial catheter. Results showed that the embolization coils, sometimes used in combination with other embolization agents, were a useful adjunct to surgery and medical management of patients.

Allison and Adam (1988) described cases of percutaneous liver biopsy followed by biopsy track embolization using steel coils. After the biopsy was performed and the needle withdrawn, there was profuse bleeding from the sheath usually because the biopsy track communicated with a portal or hepatic radicle. A specially designed needle carrying a preloaded embolization coil was inserted into the sheath and the coil was deposited into a biopsy track close to the point of communication between the track and the damaged vein resulting in hemostasis within 1-2 minutes. The sheath was gradually withdrawn and more contrast medium was injected to demonstrate any other communications

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between the track and hepatic blood vessels. On average, two coils were used for embolization in each patient. No complications attributable to the procedure were observed. These authors believe that the use of steel coils will make percutaneous biopsy in high risk patients safer and simpler and will allow a histologic diagnosis to be made in many cases where otherwise not possible.

White et al. (1988) described embolizations of 276 pulmonary arteriovenous malformations (PAVMs) over a 10 year period. Improved techniques for embolotherapy of PAVMs was described using detachable balloons that were sometimes used in combination with stainless steel coils. Detachable balloons were used alone to occlude 266 PAVMs. A single large balloon placed in a stainless steel coil matrix provided final occlusion in 10 large PAVMs (arteries exceeding 9mm in diameter). In the very large PAVMs, nests of coils were formed first with 10, 12 or 15mm stainless steel coils interspersed with 8 and 5mm stainless steel coils. Placement of oversized coils followed by placement of smaller ones formed a scaffolding distally in the branch artery supplying the PAVM. Then, to effect permanent occlusion, a large balloon was placed proximally in the coils.

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Chuang et al. (1981) reviewed complications of coil embolization using 1200 steel coils from 1975 to 1980 which were placed for vascular occlusion. Three types of coils were described. The original coil, used from 1975 to 1978, was made from a 5cm curled segment of .097mm guide wire. Wool and later Dacron strands were attached to the proximal tip of the coil to facilitate clot formation. Another type, the mini-coil, was introduced in 1978 to be delivered through a non-tapered 5 French polyethylene catheter for the occlusion of smaller arteries. The mini-coil was made from a 5cm segment of 0.52mm stainless steel guide wire with a 3mm adaptor made of 0.81mm guide wire attached to both ends; the amount of Dacron strands was less than that on the original coil. The third type of coil was introduced in 1980 and was designed for use through 5 French polyethylene and 6.5 French torque catheters with the tips tapered to a 0.97mm guide wire. This coil differed in that the Dacron strands were evenly distributed throughout the first 4cm of the 5cm segment of 0.71mm guide wire. The new version did not require a special introducer and was inserted and passed through the catheters with a standard 0.97mm guide wire (coils were available in helix diameters of 3, 5 and 8mm). Of 1200 coils,

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there were only eight noteworthy complications: two coils were lost and retrieved; one coil was lost (remaining in the distal pulmonary circulation); four coils were misplaced to undesired sites, and one coil was fragmented and displaced during surgery. In the first case, the coil was lost in the abdominal aorta during infarction of a renal carcinoma. In the second case, an original coil was jammed at the tip of a catheter during embolization. In both cases, the coil was retrieved using a Dormier basket. In the third case, high flow dislodged the coil and carried it into the left lower lobe pulmonary artery without the patient developing any respiratory symptoms. In four cases, coils were misplaced in the hepatic arteries. The patients suffered no sequelae from the coils placed in these undesired sights. In the final complication case, a coil was displaced during surgery and arteriography demonstrated a part of a coil occluding the left common iliac artery. No persistent pain or obvious consequences resulted. These authors felt that the incidence of 8 complications out of 1200 coil insertions was acceptable and that these complications can be prevented by strict adherence to the recommendations for the use of coils and use of specific catheters.

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None of the complications were life threatening and the new coil design attempts to solve these problems while accomplishing the central vascular occlusion in a safe and efficient manner.

In summary, the use of coil embolization devices was first reported in 1975 (Gianturco et al.) for the occlusion of canine coronary, celiac, superior mesenteric, renal, hepatic, splenic, carotid and iliac arteries and in one clinical case for preoperative occlusion of the renal artery. Since that time, coils have been used for arterial occlusion of bleeding abdominal tumors (Goldstein et al., 1976, Wallace et al., 1976), for the treatment of pulmonary AVMs (Taylor et al., 1978, Lois et al., 1988, White et al., 1988), for embolization of congenital thoracic vascular anomalies in infants and children (Fuhrman et al., 1984) and for embolization of the liver biopsy track (Allison and Adam, 1988). In general, it was felt that meticulous catheter technique minimizes complications. The catheter must be properly and securely placed well into the vessel to be occluded. The helical diameter of the coil should match the diameter of the vessel to be occluded since a coil too large may elongate and perhaps protrude from the vessel origin and a coil too small may travel

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distally with the blood flow or float precariously. Occlusion may not be accomplished with a single coil; segments of gelfoam may be interspersed between the coils, or smaller coils may be imbedded in larger coils to insure complete obstruction.

Thus far, a review of the literature has shown the feasibility of embolization of areas in the brain and of the use of microcoils as an embolizing agent in other areas. The following section pertains specifically to embolization in areas of the nervous system using microcoils.

H.1.3 Review of Therapeutic Embolization in Areas of the Brain, Spinal Cord and Spine Using Microcoils

Han et al. (1982) described a case report of embolization of a dural AVM using Gianturco coils. The external carotid artery, the major feeding artery to the AVM, was selectively catheterized and a 3mm mini Gianturco coil was introduced through a 5 French catheter. Post-embolization external carotid arteriography showed complete occlusion of the middle meningeal artery. Five days later a frontotemporal craniotomy was performed and the residual dural AVM was exposed. An 18 gauge needle was directly inserted into the aneurysmal venous sac and 8mm Gianturco coils were introduced. Following this, 5mm and 3mm coils were injected.

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A total of 18 coils were introduced until there was no blood return through the needle. Post-operative arteriography showed the dural AVM to be completely occluded by the coils.

As reported by Mickle and Quisling (1986), surgical excision remains the best mode of therapy for most AVMs of the brain. Vein of Galen malformations, however, do not lend themselves to excision because they are deep midline shunts. An interventional method of treatment was attempted in three patients to reduce the shunt in the vein of Galen using embolization. These authors elected to use Gianturco coil spring emboli to provide a gradual reduction in blood flow. An angiographic catheter was placed within the center of the aneurysm and four to eight 15mm Gianturco coils were inserted in each of the three patients to reduce the regional flow through the shunt by approximately one-half in the first stage of treatment. In the second stage of treatment, the patient underwent embolization 3-21 days after the initial procedure, if needed, to completely eliminate flow through the vein of Galen aneurysm. An average of 14-17 coils was required to accomplish complete occlusion in each patient. These authors showed the feasibility of embolization with microcoils providing

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progressive thrombosis of a high-flow fistulous condition and resulting in rapid metabolic improvement in the gravely ill neonate harboring a high-flow vein of Galen shunt.

Han et al. (1987) reported on the diagnosis and treatment of a lumbar extradural AVM using Gianturco coils by selectively catheterizing the lumbar artery. Due to the size of this feeding artery and resultant high speed flow, a large 8mm Gianturco coil was required for initial hemostasis. Additional coils were injected (two 8mm coils followed by three 5mm coils) and minimal residual flow through the lesion was evident. Complete occlusion was achieved by inserting a final 5mm coil. Embolization resulted in complete relief of the patient's leg pain.

Higashida et al. (1989) described interventional neurovascular treatment of traumatic carotid and vertebral artery lesions using embolization therapy. Over a period of 14 years, 234 consecutive cases of traumatic injuries to the carotid or vertebral arteries were evaluated by this group for intravascular embolization therapy. The embolization device for the majority of these patients was a detachable balloon, although liquid tissue adhesives, microcoils, and silk suture were

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also used. The goal of treatment was fistula occlusion and preservation of the parent vessel which was achieved in 82% of the cases.

In summary, these four studies describe therapeutic embolization using microcoils in areas of the nervous system including treatments of a dural AVM (Han et al., 1982), three vein of Galen malformations (Mickle and Quisling, 1983) and nine (of 234) traumatic carotid and vertebral artery lesions (Higashida et al., 1989). Results from these studies suggest that the comparable Hilal Microcoil™ has a reasonable assurance of safety and efficacy as an embolization product in the nervous system.

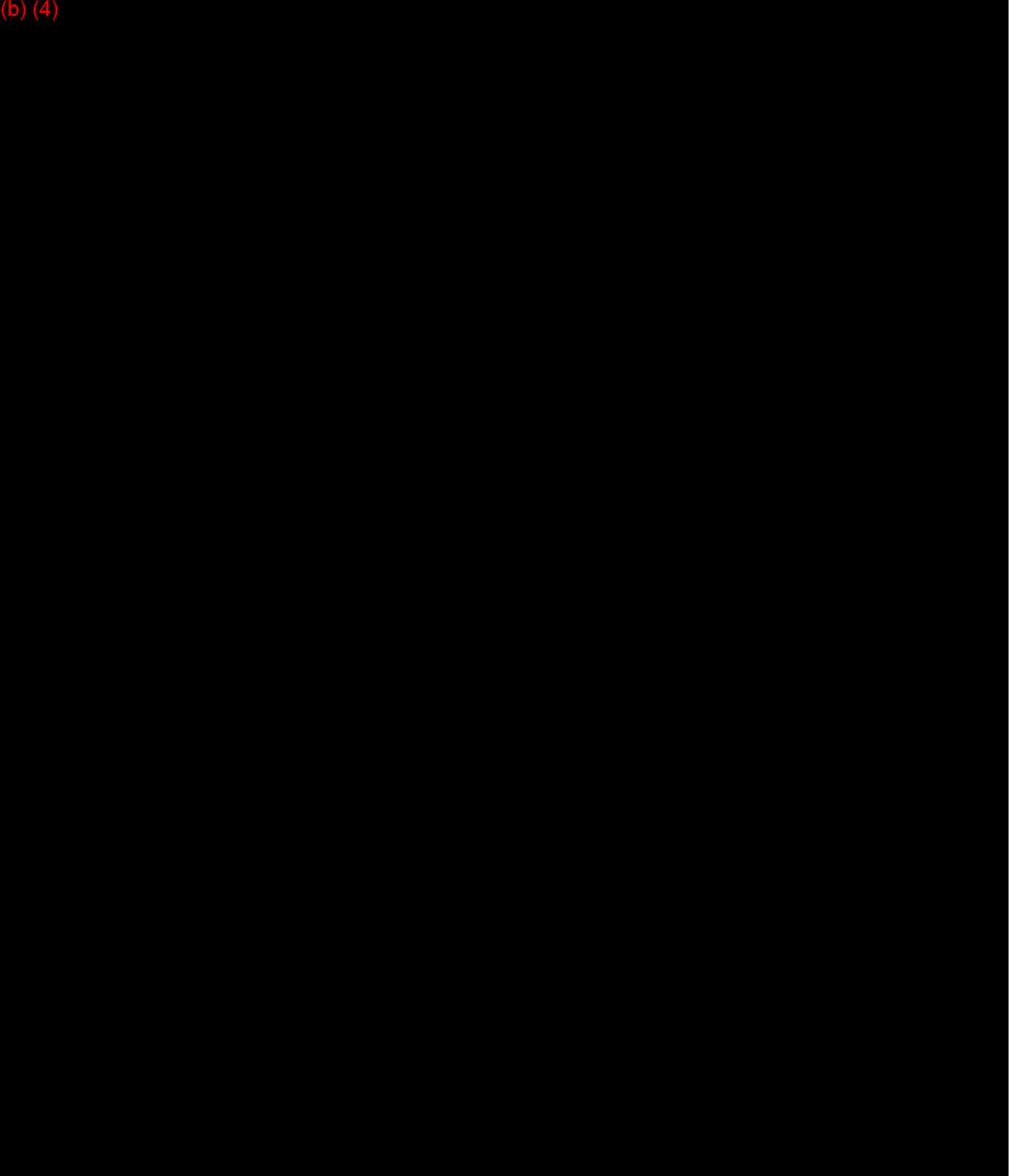
H.1.4 Summary of Literature Review

Early studies show the use of silastic beads, gelfoam, liquid adhesives and coils as embolization agents. Animal and human studies using the microcoils for treatment of various AVMs show beneficial results. Microcoils, unlike silastic beads, gelfoam or liquid adhesives, will not dissolve with time nor is there a high risk of migration. In studies using microcoils, desired placement was shown to be achievable with relative ease. Use of the comparable Hilal Microcoil™ in

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specific areas of the brain, spinal cord, and spine
is described as follows.

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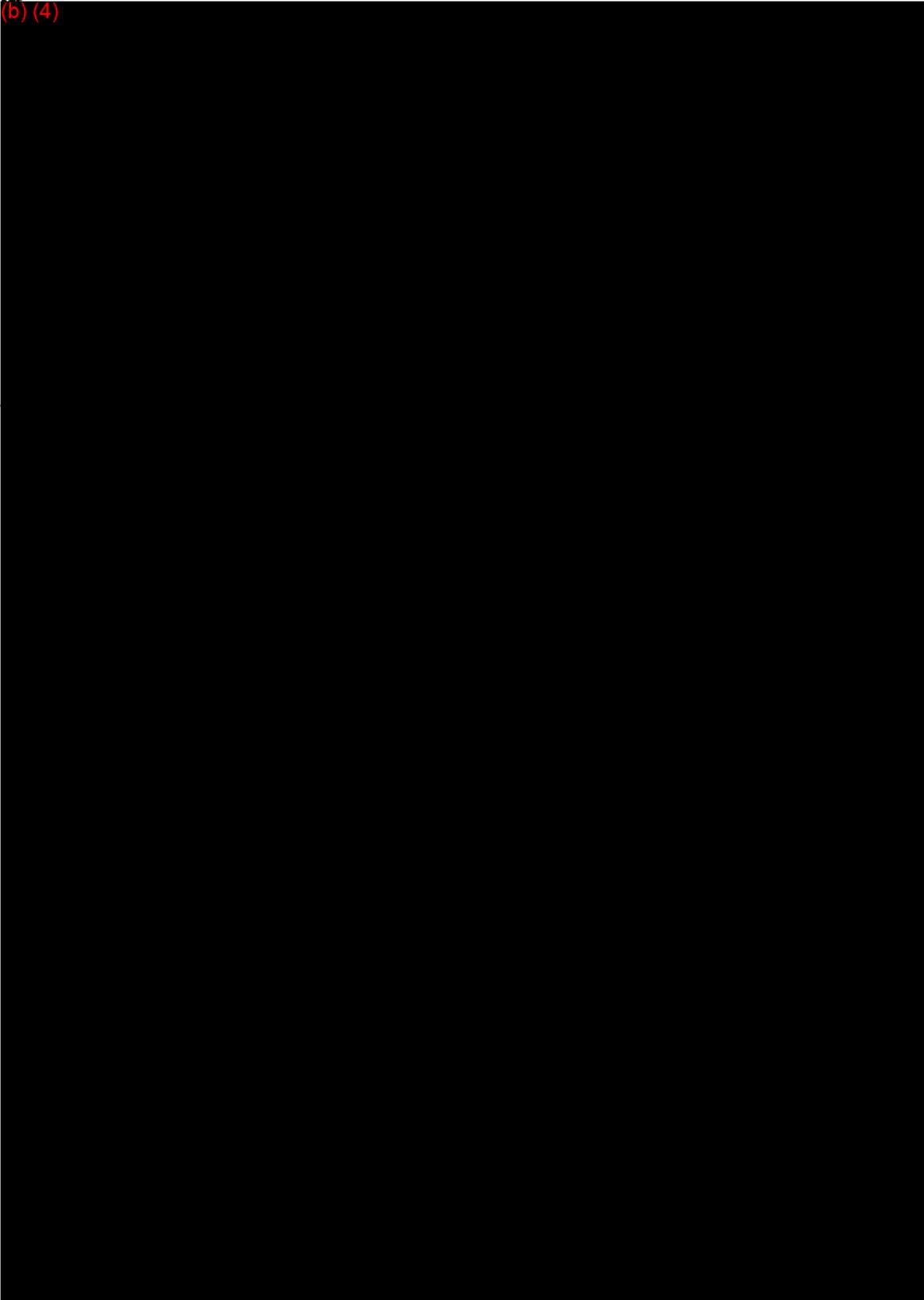


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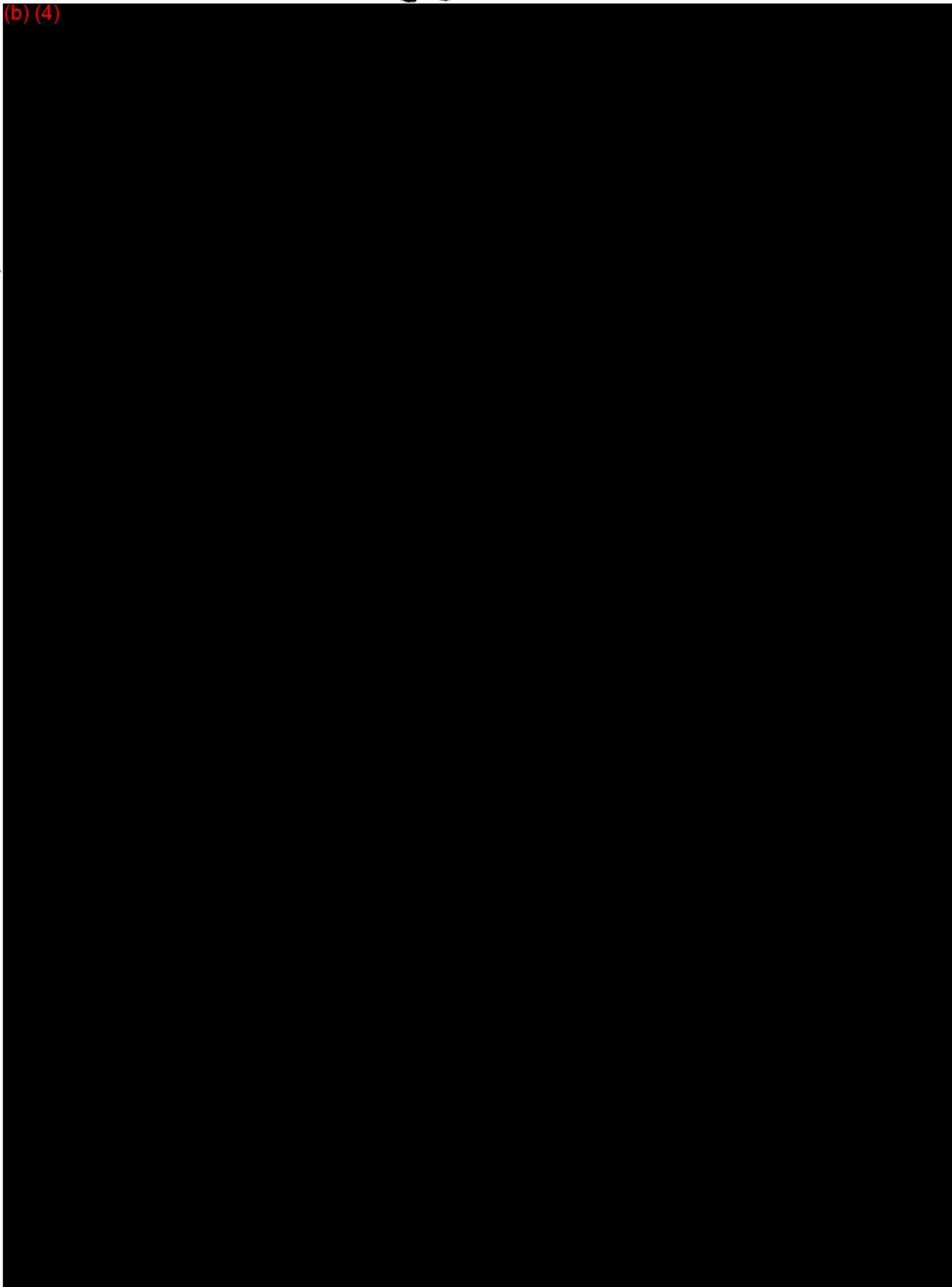
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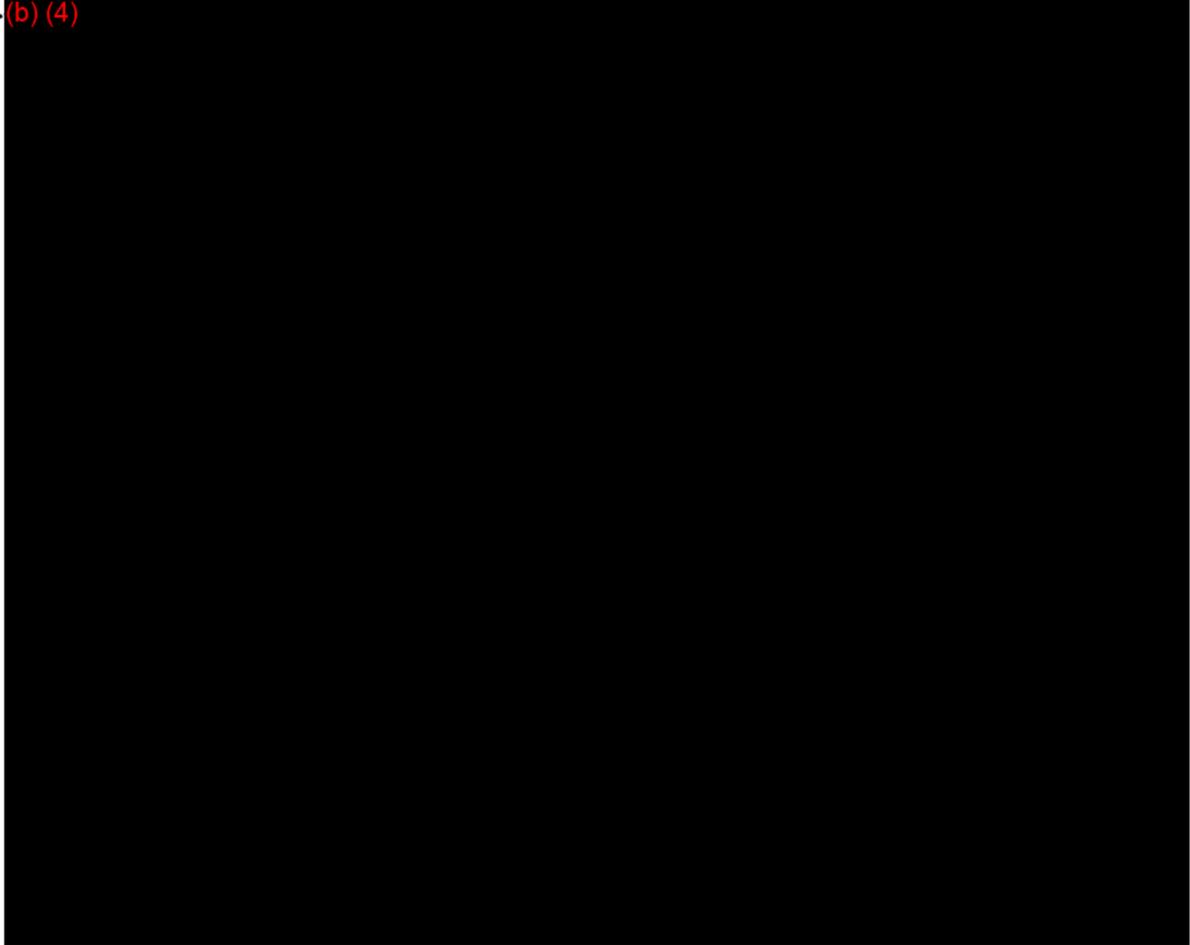


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EXHIBIT

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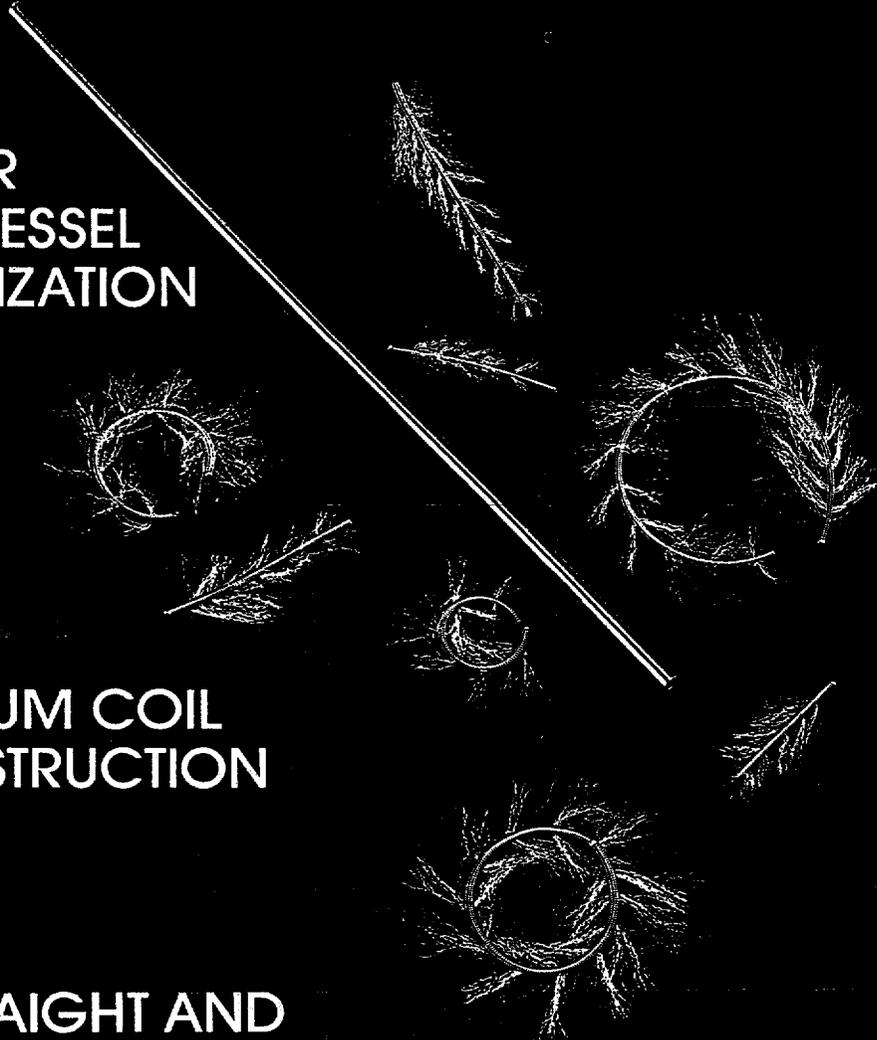
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HILAL EMBOLIZATION MICROCOILS™

- IDEAL FOR
SMALL VESSEL
EMBOLIZATION

- PLATINUM COIL
CONSTRUCTION

- STRAIGHT AND
CURLED DESIGNS



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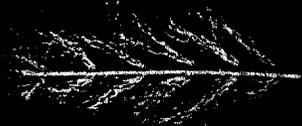
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HILAL EMBOLIZATION MICROCOILS™

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STRAIGHT

Used for embolization of selective vessel supply to arterio-venous malformations and other vascular lesions of the brain, spinal cord and spine. Design of the Microcoils™ permits introduction through small, pre-positioned delivery catheters. Unique, straight, non-curling design permits delivery into the target vessel by saline flush after initial advancement through the straightest segment of the catheter using the wire guide. The coils are made of platinum, easily detected radiographically, with spaced synthetic fibers to promote maximum thrombogenicity. **NOTE:** Microcoils™ may be used in conjunction with particulate or liquid embolization materials. Final positioning of Microcoils™ creates a "platinum cast" effect within the vessel lumen. Supplied sterile in peel-open packages. Intended for one-time use.



MICROCOIL™
Platinum with synthetic fibers

ORDER NUMBER	Length ¹	Configuration	Remarks
MWCE-18-0.5-0-HILAL	.5 cm	Straight	
MWCE-18-0.7-0-HILAL	.7 cm	Straight	Supplied 2 each per package
MWCE-18-1.0-0-HILAL	1.0 cm	Straight	
MWCE-18-1.5-0-HILAL	1.5 cm	Straight	

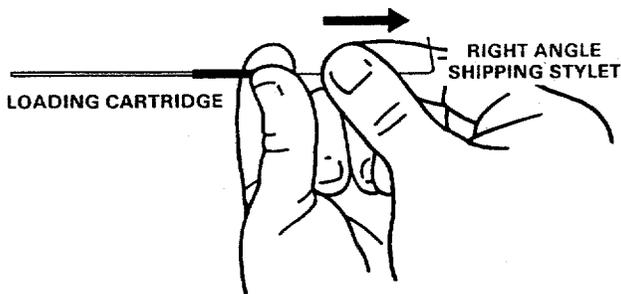
¹Other coil lengths available upon request

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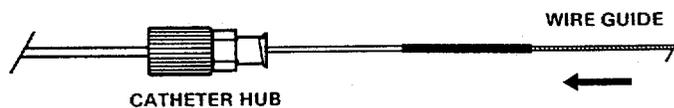
DELIVERY CATHETER AND WIRE GUIDE RECOMMENDATIONS FOR STRAIGHT AND CURLED MICROCOILS™

- Microcoils™ are recommended for use through catheters designed for use with .018 inch (0.46 mm) diameter wire guides and whose inner diameter (ID) does not exceed .027 inch (0.69 mm) diameter. **NOTE:** Cook catheters appropriate for use are non-tapered T3.0 and T3.0S Teflon® catheters.
- Microcoils™ are not recommended for use with polyurethane or polyvinylchloride catheters.
- Wire guides recommended for loading and positioning Microcoils™ are Teflon® coated .018 inch (0.46 mm) diameter with flexible tapered tips. **NOTE:** Cook Order Numbers: **TSFNA-18-180, TSFNB-18-180.**

TO LOAD MICROCOIL™ INTO DELIVERY CATHETER



3. Position loading cartridge into base of hub of catheter.



4. Using .018 inch (0.46 mm) diameter wire guide, push Microcoil™ out of loading cartridge and into catheter lumen.

5. Remove loading cartridge.

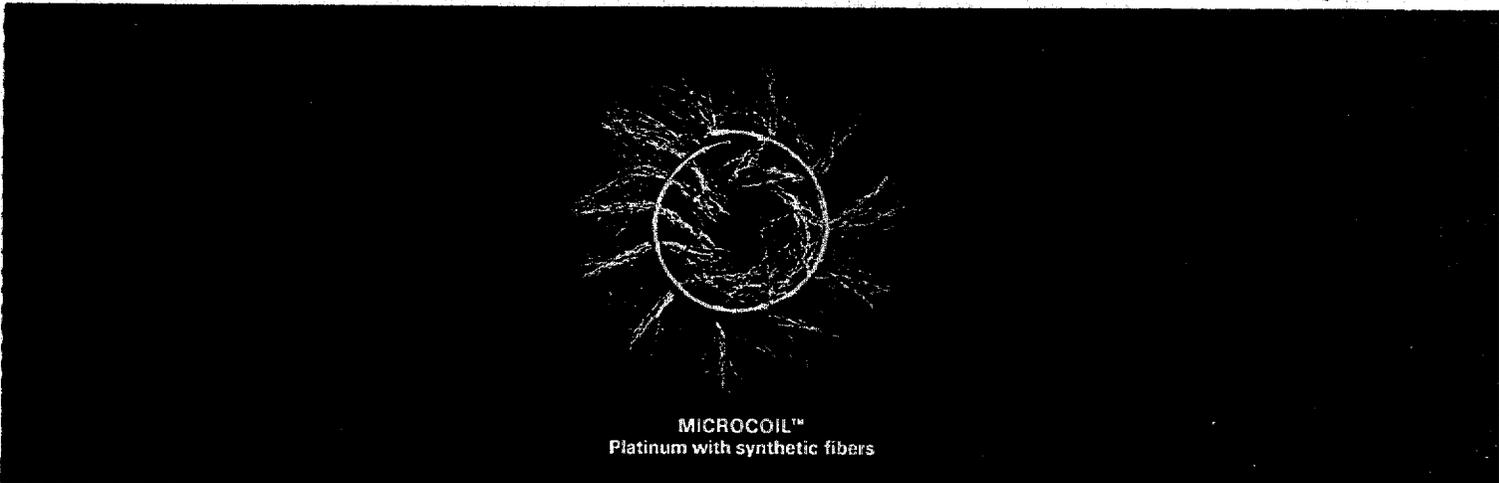
1. Firmly grasp Microcoil™ loading cartridge between thumb and forefinger at point where right angle shipping stylet exits.
2. While maintaining firm finger grip, remove shipping stylet. This will prevent Microcoil™ from exiting cartridge. Verify its position inside cartridge by direct vision.

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HILAL EMBOLIZATION MICROCOILS™

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Used for arterial and venous embolization procedures. Design of the Microcoils™ permits introduction through small pre-positioned delivery catheters. Deployment of coils into the vessel lumen is accomplished utilizing standard wire guide pusher techniques. The coils are made of platinum, easily detected radiographically, with spaced synthetic fibers to promote maximum thrombogenicity. **NOTE:** Microcoils™ may be used with particulate or liquid embolization materials. Supplied sterile in peel-open packages. Intended for one-time use.



ORDER NUMBER	Curled Diameter	Length	Configuration	Remarks
NCE-18-1.0-3-HILAL	3 mm	1.0 cm	Curled	
MWCE-18-1.5-5-HILAL	5 mm	1.5 cm	Curled	
MWCE-18-2.1-7-HILAL	7 mm	2.1 cm	Curled	Supplied 2 each per package
MWCE-18-3.0-10-HILAL	10 mm	3.0 cm	Curled	

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REFERENCES

S. Hilal, M.D., Department of Radiology, The Neurological Institute, New York, New York.

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V. P. Chuang, S. Wallace, C. Gianturco: "A New Improved Coil for Tapered Tip Catheter for Arterial Occlusion," *Radiology*, 135 (1980), 507-509.

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A COOK GROUP COMPANY
P.O. Box 489
Bloomington, IN 47402 U.S.A.
Phone: 812 339-2235
Toll Free: 800 457-4500

COOK (CANADA) INC.
A COOK GROUP COMPANY
111 Sandiford Drive
Stouffville, Ontario L4A 7X5 CANADA
Phone: 416 640-7110
Toll Free: 800 668-0300

WILLIAM A. COOK AUSTRALIA PTY. LTD.
A COOK GROUP COMPANY
Brisbane Technology Park
12 Electronics Street
Eight Mile Plains
Brisbane, QLD 4113 AUSTRALIA
Phone: 07 841-1188

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**INTENDED FOR ONE-TIME USE. STERILE IF PACKAGE IS UNOPENED OR UNDAMAGED.
STERILIZATION LOT NUMBER ON BACK OF PACKAGE. Federal (U.S.A.) law restricts this
device to use by or at the direction of a physician.**

REORDER# MWCE-18-1.5-0-HILAL
HILAL EMBOLIZATION MICROCOILSTM
1.5CM, STRAIGHT
WARNING: NOT RECOMMENDED FOR USE WITH
POLYURETHANE OR POLYVINYLCHLORIDE
CATHETERS. COILS MAY BECOME LODGED
IN LUMEN.
LOT NO. SAMPLE

CC6 287

A Cook Group Company
P.O. Box 489 Bloomington, IN 47402 USA



**WARNING:
DO NOT SHORTEN LENGTH
OF MICROCOILTM BY CUTTING.**

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STERILIZATION LOT NUMBER ON BACK OF PACKAGE. Federal (U.S.A.) law restricts this
device to sale by or on the order of a physician.

REORDER# MWCE-18-1.0-3-HILAL
HILAL EMBOLIZATION MICROCOILS TM
1.0CM LONG, 3MM DIAMETER

WARNING: NOT RECOMMENDED FOR USE WITH
POLYURETHANE OR POLYVINYLCHLORIDE
CATHETERS, COILS MAY BECOME LODGED
IN LUMEN

LOT NO. 228600

CC6 788

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EXHIBIT

EXHIBIT II

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STERILIZATION LOT NUMBER ON BACK OF PACKAGE. Federal (U.S.A.) law restricts this
device to use by or at the direction of a physician.

REORDER# MWCE-38-4-3
OCCLUDING SPRING EMBOLI
4CM LONG, 3MM DIAMETER

WARNING: NOT RECOMMENDED FOR USE WITH
POLYURETHANE OR POLYVINYLCHLORIDE
CATHETER, COILS MAY BECOME LODGED
IN LUMEN

LOT NO. TEST. 39027

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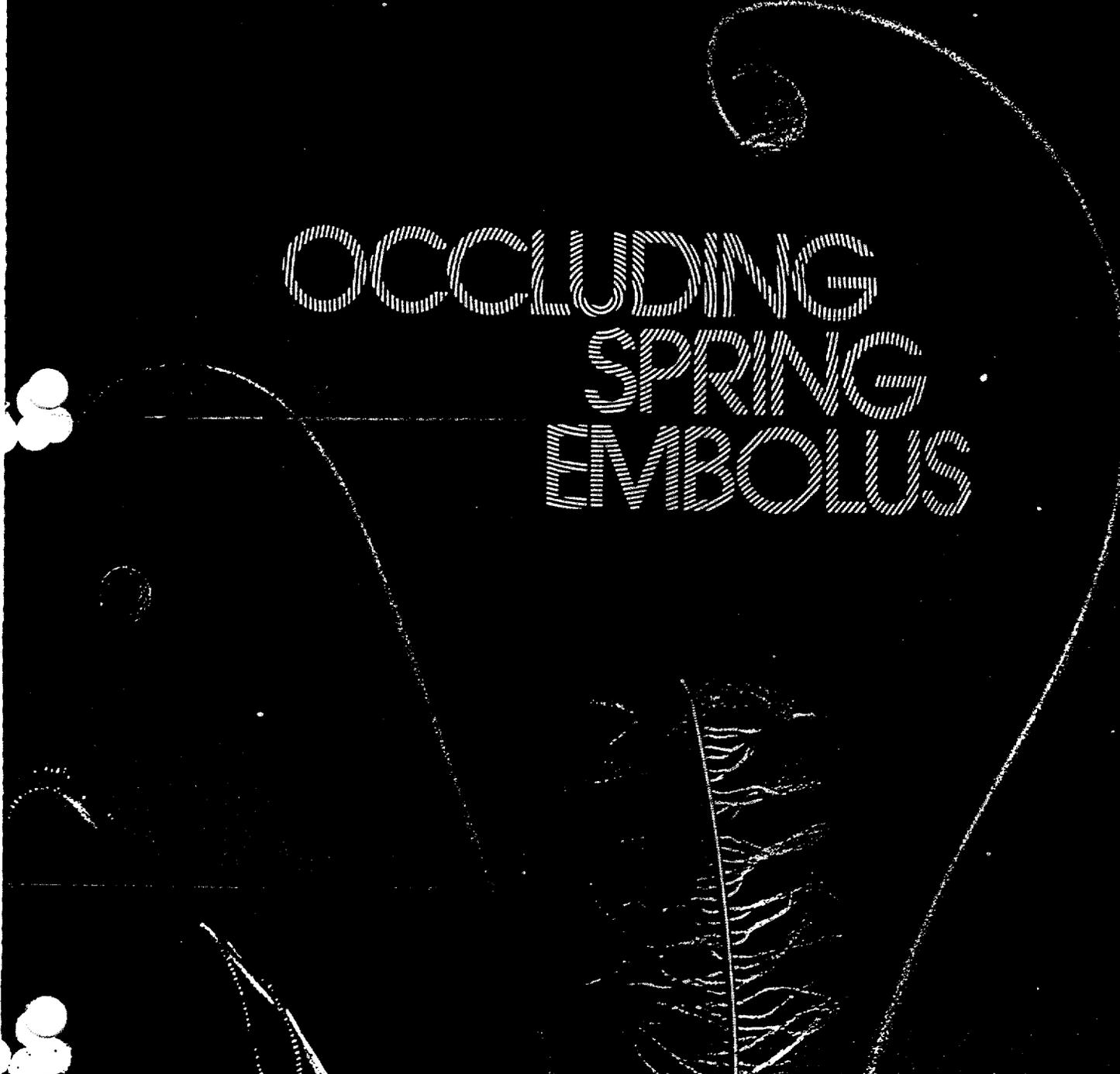


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COOK

Cook Incorporated



OCCCLUDING
SPRING
EMBOLUS

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CONFIDENTIAL**SUGGESTED INSTRUCTIONS FOR USING OCCLUDING SPRING EMBOLUS**

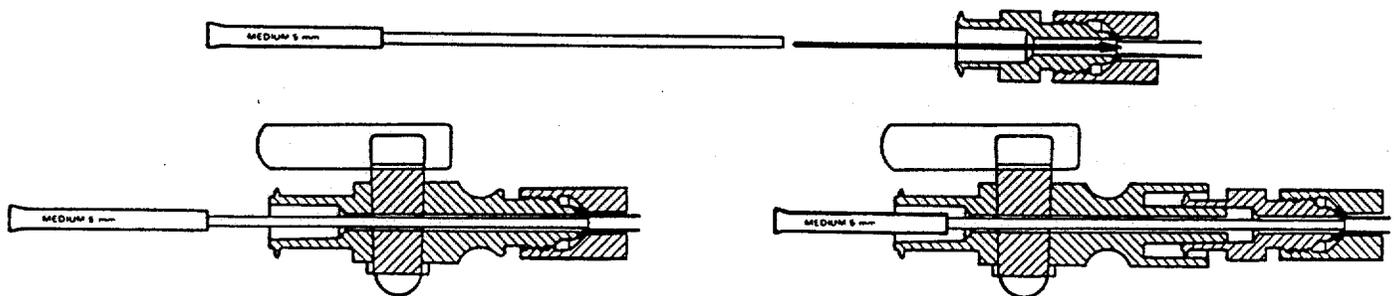
CATALOG NUMBER	Diameter of Coiled Spring Embolus mm	Color Code of Cartridge
MWCE-38-4-3	3	Black
MWCE-38-5-5	5	Blue
MWCE-38-5-8	8	Red

These occluding spring emboli are designed to be used with 6.5 French TORCON and 5.0M French (COOK) polyethylene catheters with tips tapered to a .038 inch (0.97 mm) wire guide.

To load the spring embolus into the catheter, insert the cartridge through the stopcock, hub, or both until it is seated on the catheter flare (see figures below). While maintaining the cartridge in this position, push the embolus into the catheter for a distance of 20-30 cm using the stiff end of a .038 inch (0.97 mm) wire guide. Remove the wire guide and cartridge.

With the soft tip of the wire guide, push the coil through the distal tip of the catheter. The ease with which the coil can be pushed through the terminal curve(s) of the catheter depends upon the flexibility of the wire guide tip. The Newton LLT (catalog number **SFNB-38-x**) is recommended for most cases; **SFNC** and **SLF** guides may be useful in some instances of excessive tortuosity of the vessels.

Gianturco, Wallace, and Chuang recommend that the last coil be positioned with particular care. This coil should not be left too close to the inlet of the artery and should be intermeshed with the previous coils if possible; it should be of sufficient size to wedge against the arterial walls. A minimal but sufficient arterial blood flow should remain to hold this coil against the previous coils or other embolic materials until a solid clot insures a permanent fixation. The purpose of these recommendations is to minimize the possibility of a loose coil becoming dislodged and obstructing a normal and essential arterial channel.

**NOTICE**

If a catheter with sideports is used, the embolus may jam in the sideport or pass through it into a location other than that intended.

REFERENCE

V. P. Chuang, S. Wallace, C. Gianturco: "A New Improved Coil for Tapered Tip Catheter for Arterial Occlusion," *Radiology*, 135 (1980), 507-509.

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A COOK GROUP COMPANY
P.O. Box 489 Bloomington, IN 47402 U.S.A.
Phone: 812.339-2235

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SPECIAL PROCEDURE SET

REORDER NUMBER: GAO 1

SUPERSELECTIVE SET

LOT NUMBER: 51833R

CAUTION: FEDERAL (U.S.A.) LAW RESTRICTS THIS DEVICE TO USE BY
OR AT DIRECTION OF A PHYSICIAN.

CI **COOK INCORPORATED**
BOX 489 BLOOMINGTON, INDIANA 47402



GREEN DOT INDICATES
ENCLOSED PRODUCT
HAS BEEN SUBJECTED TO
A STERILIZING CYCLE

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(b)(4) Trade Secret Process- Product Specs

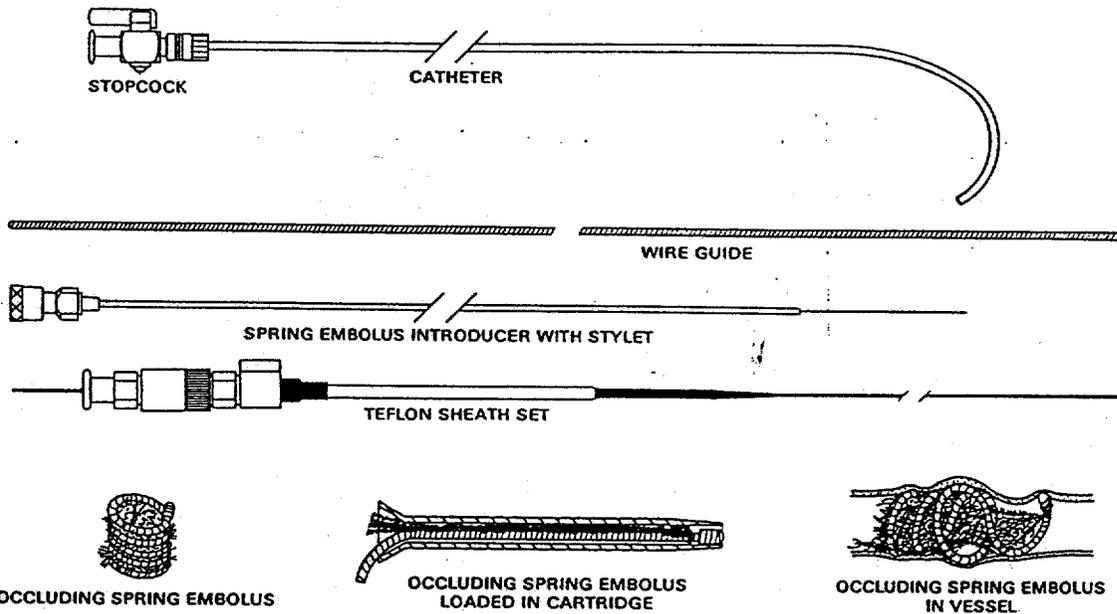


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GIANTURCO-WALLACE-ANDERSON ARTERIAL EMBOLIZATION SET Sterile



Used for transcatheter embolization of visceral arteries.

CATALOG NUMBER	Description
GAO-1	SET consists of 7 French catheter, wire guide, introducer with stylet and ten occluding spring emboli. Complete description of components is listed below.
T7.0-NT-60.5-MST-NS-GAO	CATHETER is 7 French radiopaque Teflon, 60.5 cm long with no sideports and metal stopcock.
SF-52-80-GAO	WIRE GUIDE is 1.32 mm (.052 inch) diameter, 80 cm long with 8 cm flexible tip and stainless steel.
EI-18-50	SPRING EMBOLUS INTRODUCER WITH STYLET
TSS-7-5-38	DESILETS-HOFFMAN SHEATH SET for catheter introduction.
WCE-35-5-7-5	OCCLUDING SPRING EMBOLUS consists of Dacron strands, 3 cm long, attached to a 5 cm segment of tightly coiled .035 inch stainless steel wire and enclosed in 7 French radiopaque Teflon cartridge. Diameter of coil is 5 mm.
GAO-3	SET consists of 5 French catheter, wire guide, introducer with stylet and ten occluding spring emboli. Complete description of components is listed below.
P5.0M-NT-100-ST-NS-2.0	CATHETER is 5 French radiopaque polyethylene, 100 cm long with no sideports and plastic stopcock.
SF-38-125	WIRE GUIDE is stainless steel .97 mm (0.038 inch) diameter, 125 cm long with 3 cm flexible tip.
EI-21-80	SPRING EMBOLUS INTRODUCER WITH STYLET
TSS-5-5-25	DESILETS-HOFFMAN SHEATH SET for catheter introduction.
WCE-21-5-5-4	OCCLUDING SPRING EMBOLUS consists of Dacron strands, 2.8 cm long, attached to a 5.5 cm segment of coiled .021 inch stainless steel wire and enclosed in 5 French radiopaque polyethylene cartridge. Diameter of coil is 4 mm.

References:

C. Gianturco, J. H. Anderson, S. Wallace: "Mechanical Devices for Arterial Occlusion," *American Journal of Roentgenology*, 124 (1975), 428-435.

H. M. Goldstein, S. Wallace, J. Anderson, R. L. Bree, C. Gianturco: "Transcatheter Occlusion of Abdominal Tumors," *Radiology*, 120 (1976), 539-545.

S. Wallace, C. Gianturco, J. Anderson, H. M. Goldstein, J. L. Davis, R. L. Bree: "Therapeutic Vascular Occlusion Utilizing Steel Coil Technique: Clinical Applications," *American Journal of Roentgenology*, 127 (1976), 381-387.

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EXHIBIT

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EXHIBIT III

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EXHIBIT

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EXHIBIT IV

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STERILIZATION
TECHNICAL
SERVICES, Inc.

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STS Report No. M-229A

Determination of Product D Value
For Cook, Inc.

Prepared for:

Mr. Ron Mobley
Cook Incorporated
925 S. Curry Pike, PO Box 489
Bloomington, Indiana 47402

Prepared by:

Sterilization Technical Services, Inc.
7500 West Henrietta Road
Rush, New York 14543

Study Conducted by:

Jean Whitmore
Jean Whitmore

James Whitbourne
James Whitbourne

Approved by:

James Whitbourne
James Whitbourne

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January 25, 1985

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~~CONFIDENTIAL~~STS Report No. M-229 A
Page 2~~CONFIDENTIAL~~Rationale:

Current GMP requires that sterilization of medical devices be done in a process that has been validated and which can be shown to be in control. Considerable latitude has been permitted with respect to what constitutes an acceptable method of validation. Many involved in sterilization of medical devices with ethylene oxide have used one of the methods described in the AAMI guideline. The current validation of Cook cycles is based upon the so called "half cycle" technique which is described in the AAMI document. While this is generally a more than adequate technique it does utilize overkill to establish cycle time. Cycle time is better derived from the standpoint of optimal exposure time, sterility assurance level (SAL) achieved and minimizing ethylene oxide residuals, by utilizing the product bioburden resistance validation method. In this procedure sublethal cycles are employed to expose actual product which is then sterility tested. This data is used, along with the bioburden, in the Halvorson-Ziegler equation to establish the D value for the particular product. Coupled with this, a biological indicator system which is capable of, at a minimum, reflecting resistance equal to a 10^{-6} SAL for the product is developed. At the onset of this study it was not known whether the sterilization cycles required to kill the bioburden plus a safety factor of 10^5 will be longer, shorter or of the same length as the current cycles validated according to the half cycle technique. However, what is more significant is that the cycles will be designed around the actual product/microorganism resistance that exists. The half cycle technique while affording a substantial safety factor will not by its nature reflect changes in bioburden resistance. Measurement of bioburden is necessary to establish that control over the manufacturing environment will not result in significant fluctuation. However, it will not measure the intrinsic resistance of that bioburden nor changes which occur only in resistance not in numbers of microorganisms. The system being studied will measure all aspects and with periodic monitoring continued, will bring to light any changes in both numbers and resistance.

Reference:

Guideline for Industrial Ethylene Oxide Sterilization of Medical Devices: Association for the Advancement of Medical Instrumentation. AAMI OPEO-12/81

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STS Report No. M-229 A
Page 3

Purpose:

To evaluate various Cook, Inc. products to determine the resistance of the product bioburden in ethylene oxide sterilization. The resistance data (D value) will be used along with a biological indicator system to establish that the sterilization process used by Cook has a SAL of a least 10^{-6} . The biological indicator system will use spore strips as the sterility release mechanism.

Material:

Tryptic Soy Broth (Difco Laboratories, Detroit, Mich.)
Standard Methods Agar (Difco Laboratories, Detroit, Mich.)
Sterile - test tubes, petri dishes and pipettes
BIER type ethylene oxide sterilizer
Cook, Inc. Medical Devices (See Table I)
Blender cups
Spore strips Lot 641 Amsco Spordex
Spore Strips Lot 648 Amsco Spordex
Laminar Flow Hood (Class 100)
Appropriate pre-sterilized materials for aseptic handling

Procedure:

1.0 Product Selection

Due to the very large number of different products requiring EO sterilization at Cook, it was necessary to evaluate the resistance of many of this group. However, similiarity between many of the products made it possible to limit the total number requiring assessment. The products which were tested were chosen as representative of a family of products. The choice of what product in a family was selected was based primarily on the factors which would make it the most difficult to sterilize such as the presence of a lumen, length etc. The primary objective is to establish which products are most resistant and establish a D value for these particular products.

2.0 Ethylene Oxide Exposure

The products were tested by exposing 10 samples per time interval to EO parameters which were similar to those used by Cook, Inc. These parameters follow:

High Temperature Exposure

Temperature - 113 - 120°F.

PreVacuum - 20-1" Hg

Relative Humidity - 80%, -10, +20%RH

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STS Report No. H-229 A

Page 4

CONFIDENTIALProcedure (cont.):Gas Concentration - 7 psig \pm 0.5 psig

Exposure Time - Variable

Low Temperature Exposure

Temperature - 84 - 89°F

PreVacuum - 20" Hg

Relative Humidity - 80%, -10, +20%RH

Gas Concentration - 5 psig

Exposure Time - Variable

The testing was done in a BIER type EO vessel which permitted control of each parameter and variation of parameters where appropriate. The cycle (exposure) time was based upon the length necessary to result in some positive samples and some negative samples when the material was sterility tested. This procedure yields a fractional result, i.e. Positive sample/Total No. samples tested. A sufficient number of these cycles are run to generate at least 3 fractional values except in those cases where product resistance is so low that useful information in these cases can not reasonably be obtained. This would not effect efficacy because the resistance is much lower than that of other products upon which the sterilization cycle is based. The products during gas exposure are packaged the same as in routine production.

Sterility testing is conducted by aseptically transferring the product, cutting where necessary, to Soybean Casein Digest Medium and incubating at 20-25°C for a minimum of 14 days. A lack of turbidity or other indications of microbiological growth at the end of the incubation period is interpreted as a negative or sterile sample.

The D value for each product is calculated by means of the Halvorson-Ziegler equation. This fraction negative equation is preferable to log reduction (kill curve) techniques because of the low level of organisms generally associated with bioburdens and it is more useful when dealing with heterogenous microbial population.

Halvorson-Ziegler Equation:

$$D = \frac{t}{\log N_0 - \log \left(\ln \frac{r}{q} \right)}$$

t=exposure time
 N₀=Bioburden value
 r=No. Sterile samples
 q=No. Samples tested

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3.0 Bioburden

For each product assessed in the study bioburden was determined by either direct analysis at the time or from historical data generated over a period of years. The general procedure involved extracting the sample in phosphate buffer containing Tween 80. The samples were agitated for 15 minutes on a mechanical shaker during extraction. Each sample was assayed for three general microbiological groupings by plating as follows:

1. Mesophylic Aerobes - Standard Methods Agar with incubation at 20-25°C
2. Spore formers - 80°C heat shock for 10 minutes, Standard Methods Agar with incubation at 32-35°C
3. Fungi - Sabourauds Dextrose Agar with incubation at 20-25°C

The total bioburden per product is characterized by summing the mesophylic aerobes and those fungi which have not appeared on the mesophylic aerobe plate. The spore count is included only if a higher recovery is found, as a result of heat shock on the spore plates. Generally any spores present will have out grown on the mesophylic aerobe plate and do not add to the total bioburden, however, a knowledge of the spore population is significant.

4.0 Selection of a Biological Indicator System

Early on in this study it was determined that a spore strip in glaseine placed in the product package would not afford sufficient resistance to insure a high enough product SAL level. Therefore studies were conducted to find a system which would be reproducible and easily obtained and used. A 10 cc syringe was chosen and the spore strip was placed between the plunger and the syringe outlet. If required, a specific gauge needle can be placed on the syringe to further increase the resistance of the system.

The D value of the system was assessed in the same high and low temperature cycles as

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used for product resistance studies. The D value of the spore strip was determined both in the syringe and outside the syringe. A kill curve was generated by plating the spore strips after exposure in sub-lethal cycles. Each spore strip was blended for 1 minute in a laboratory Waring Blender cup and serial dilutions pipeted into sterile petri dishes. These were overpoured with Standard Methods agar and incubated at 32-35°C until colonies developed. The data was analyzed by regression analysis to determine the D value.

5.0 Comparison of Product and BI System Resistance

Spore strips used to monitor a sterilization process are resistant to the sterilization agent employed. However, the placement of the BI is important in order to reflect a resistance which will be adequate and insure that the product is sufficiently exposed to render it sterile by current definition. This definition requires that the equivalent of a six log kill beyond that of the product bioburden be demonstrated. This is shown in the following basic equation:

$$t = \log N_0(D_p) + 6D_p \quad (\text{Equation 1})$$

Where t=time

N₀=bioburden or population

D=Product D value as determined experimentally

Therefore, if a product has been found to have a D value of 5 and a bioburden of 10, t=35. Thus a Biological Indicator with a population of 10⁶ spores would need a D=5.83 to show equivalent resistance. This calculation is shown as follows:

$$t = 6D_{ss} \quad (\text{Equation 2})$$

$$35 = 6D_{ss}$$

$$D_{ss} = 5.83 \quad (\text{In this case D must be } \geq 5.83)$$

With the knowledge of what product or products have the highest resistance (greatest D) we are able to determine what minimum resistance the Biological Indicators must have. Thus substituting equation 2 into equation 1 will yield the D value the BI system * must have.

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* Assumes that the spore strip in the BI system has a population of 10⁶

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CONFIDENTIAL**5.0 Comparison of Product and BI System Resistance (Cont.)**

to adequately monitor the desired SAL.

$$6D_{ss} = \log N_0 (D_p \text{ Equation 3})$$

The BI system will then be the only test necessary to assess sterility and provide release of sterile product.

- 1.0 The following table presents a summary of the exposure intervals, D values determined, bioburden and average D value for the products tested.

Table I
D Value Found at Variable Exposure Times (min.)

Product	Study Temperature	Time														Bioburden	Average D Value	
		2	5	7	10	15	20	25	30	33	35	40	45	50	55			60
Torcon Closed End	115	4.7	7.5	8.7		10.6											8	7.8
Teflon Coated Wire Guide	115				7.6	13	15.3	19.1	AN ⁽¹⁾		23.9		AN		AN		32	17.8
Check Flow Sheath Set	115	1.6	3.6	4.9	6.4	7.1											13.2	4.7
MWCE	115	1.3	2.5	3.5	6.7	8.8											11.3	4.6
Angiographic Catheter (Type PI)	115					10.2		15.6		19.9							20.3	15.2
Fig-Tail Catheter	115				AP ⁽²⁾	8.9		9.5		AN	AN						45	9.2
Fig-Tail Catheter	87	AP	AP		AP	AP							26.6		20.9	AN*	45	23.75
Stopcock	115				18.9	22.7		18			AN						5.5	19.9
Stopcock	87					28		14.5		AN							5.5	21.3
Two Part Needle	115				5.1	7.7	11				14.5						60.5	9.6
Balloon Catheter	115					5.2	6.5		10.3					AN			138	7.3
Sleeve Assembly	115		2.6					AN	AN								1	2.6
Disposable Needle	115						17.4		23.6		AN						10.3	20.5
Connecting Tube	87				AP	27.3	29.4		17.2								5.7	24.6
Kay Nephrostomy Tamponade Catheter	87					12.2	14.7	18.4	18.8		18.5						27.6	16.5
Malecot with Stylet	87				24.4	22.8	18.7	19.7		21.9							4.2	21.5
Facial Dilator	87				13.0	19.5	15.7										9.6	16.1
Stone Extractor	87				13.3	17.2		16.9		23.6							6.7	17.0

(1) AN - all samples tested were negative (sterile)

(2) AP - all samples tested were positive (non-sterile)

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Results (cont.): 2.0 Spore Strip Resistance

Table II

<u>Temperature</u>	<u>Lot No.</u>	<u>Configuration</u>	<u>D value</u>
High	641	In Syringe/ Needle	50.0
High	641	In Product Pkg.	11.1
High	641	In Syringe	25.0
Low	641	In Product Pkg.	25.0
Low	641	In Syringe	33.3

3.0 Calculation of Required BI System Resistance

The products found to have the highest resistance at 115°F were the stopcocks and the Disposable Needle. At 87°F the Connecting Tube, Pig Tail Catheter and Malecot with Stylet had the highest product D value. Substitution of these values into equation three (3) permits us to assess the resistance the BI system must have to provide the necessary SAL.

<u>Device</u>	<u>Temperature</u>	<u>Minimum Required BI</u>	<u>D value</u>
Stopcock	115°F	22.4	
Disposable Needle	115°F	23.9	
Pig Tail Catheter	87°F	31.4	
Connecting Tube	87°F	27.7	
Malecot w Stylet	87°F	23.7	

Thus the D value for the BI system at 115°F must be approximately 24 or greater and the D value at 87°F for the BI system must be approximately 31.4 or greater. Some products tested in this study are generally sterilized at the higher temperature, but were tested at the lower temperature. However, as the D would be less at the higher temperature and that found in the worst case, the Connecting Tube, when tested at 87°F was approximately equal to that for the minimum BI D value at 115°F, it is safe to assume that the SAL reflected at the higher temperature will be more than adequate.

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Discussion:

Selected Cook, Inc. medical devices have been evaluated by bioburden and D value assessments to validate the use of a Biological Indicator System utilizing spore strips as the sterility release mechanism. These studies have shown that the most resistant product at the two temperatures employed are the disposable needle at 115°F and pig tail catheter at 87°F. Therefore a BI system must be defined which will yield the appropriate resistance. These studies have also shown that a 10 cc syringe with no needle on and with a needle present will increase the resistance of a spore strip to a value which exceeds the needed resistance.

Therefore an appropriate BI system can be selected and will utilize spore strips as the release mechanism.

Further, these studies have been done at a lower gas concentration which will permit Cook, Inc. to initiate sterilization at these lower concentrations if they so desire. This will reduce potential EO residuals in the product and in the work environment and result in a cost savings.

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EXHIBIT

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EXHIBIT VI

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MECHANICAL DEVICES FOR ARTERIAL OCCLUSION

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HOUSTON, TEXAS

1975

TRANSCATHETER arterial embolization has had an increasing application in the control of bleeding of non-neoplastic origin; *i.e.*, gastrointestinal bleeding,^{1,2,22,27,28} traumatic renal³ and pelvic bleeding,^{21,26} hemoptysis²⁴ and epistaxis.²⁹ This approach has also been utilized in the treatment of tumors¹⁸ and arteriovenous malformation^{6,7,13,17,20} of the central nervous system; bleeding gastrointestinal¹¹ and uterine neoplasms,¹¹ and the preoperative and palliative management of renal carcinomas.^{1,12,15} The materials used for embolization include autologous tissue and clot,^{1,25,31} clot augmented by thrombin, platelets,^{4,5,11} etc., gel foam,¹² metallic and silastic spheres,¹⁴ a variety of silicone preparations,^{8,19} isobutyl-2-cyanoacrylate,⁹ and radioactive particles.¹⁶ In the search for safer, more permanent, and easily injectable materials, two mechanical devices for the embolization of small and large arteries are described in this presentation.

MATERIAL AND METHOD

In view of the requirements created by different arterial-diameters and the necessity for both central and peripheral occlusions, 2 types of mechanical occluding devices were formulated; cotton tails for smaller arteries; and wool coils for larger vessels.

COTTON TAILS

These emboli consist of 3 mm. segments of No. 19 gauge steel tubing to which are attached 8 strands of cotton threads, 5 mm. in length (Fig. 1).

A preshaped No. 6 French polyethylene catheter of uniform internal diameter with a non-tapered tip was introduced into the surgically exposed femoral artery of 10 anesthetized dogs. Selective catheterization of the artery to be embolized was accomplished. The catheter was then gently kinked approximately 10 cm. from the stopcock, obstructing reflux of blood. The cotton tails were impaled on the centrally tapered mandril of a No. 20 gauge Karras needle and inserted into the catheter through the opened stopcock. The mandril and then the needle were withdrawn leaving the embolus in place in the catheter. A syringe containing saline was attached and the lumen of the catheter was reopened by straightening the catheter. Saline was injected to push the cotton tail through the catheter into the artery (Fig. 2). The embolus was transported by the blood stream along the direction of greatest flow until it lodged in a small artery or at a bifurcation. This usually occurred when

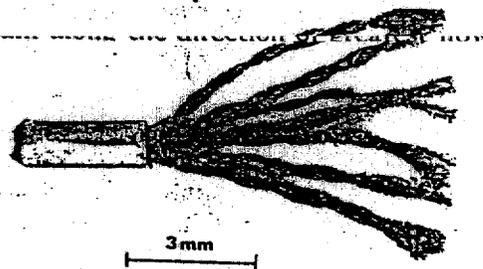


FIG. 1. The No. 19 gauge steel tubing is 3 mm. in length, and the cotton threads are 5 mm. in length.

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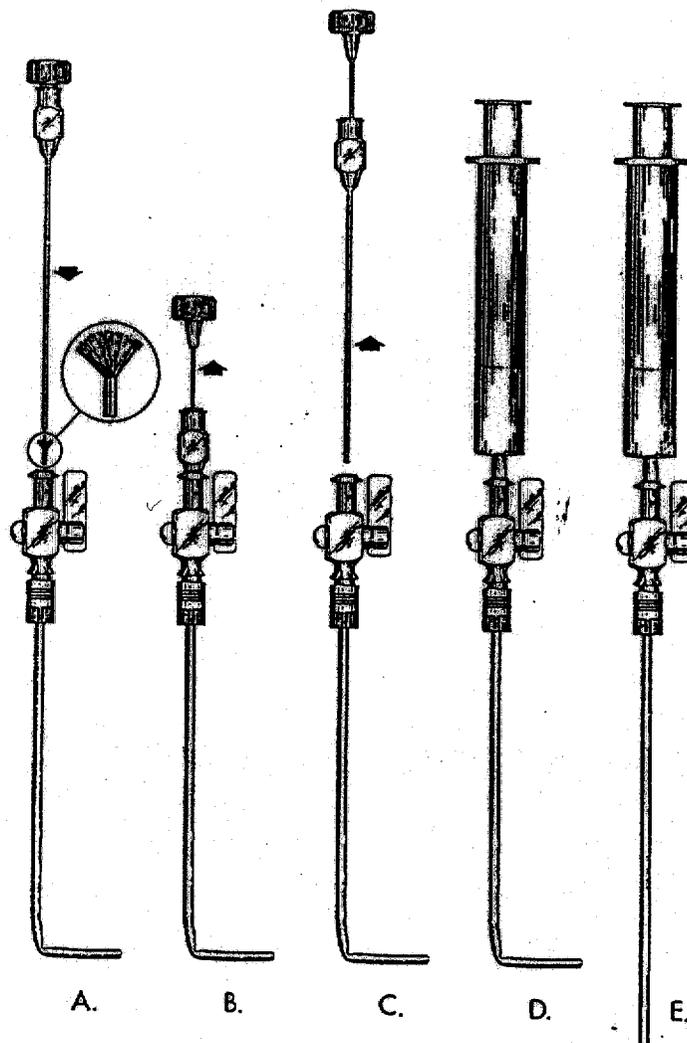


FIG. 2. Technique for embolization of cotton tail.

the arterial diameter was 2 mm. or less. This technique has been employed in dogs to occlude branches of the coronary, renal, celiac and superior mesenteric arteries (Fig. 3).

WOOL COILS

These devices for the occlusion of larger arteries were constructed by attaching 4 woolen strands, 3 cm. long, to a tightly coiled 5 cm. long segment of steel guidewire from which the central core had been removed (Fig. 4).

A preshaped No. 7 French thinwall

Teflon catheter with uniform inner diameter and non-tapered tip was introduced into the surgically exposed femoral artery of 10 anesthetized dogs. The arteries to be embolized were selectively catheterized. To facilitate passage through the Teflon catheter these steel coils with woolen tails were straightened by an introducer. The introducer consisted of a fine wire mandril protruding from a long piece of No. 19 gauge steel tubing which fit inside the catheter and was long enough to deposit the coil near the terminal curve of the catheter. The coil was left within the catheter by withdrawing

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FIG. 3. Embolization of cotton tails.

(A) Canine renal arteries embolized with cotton tails.

(B) Canine coronary artery embolized with cotton tail.

Note the peripheral position.

the mandril and the introducer. The coil was then pushed into the arterial lumen with a modified 0.045 inch guidewire. The

wool coil formed an embolus of steel and wool at a point immediately distal to the catheter tip (Fig. 5).

This device has been used to occlude canine superior mesenteric, renal, hepatic, splenic, carotid and iliac arteries (Fig. 6). Re-examination 2 weeks after the procedure revealed persistent occlusion.

ILLUSTRATIVE CLINICAL CASE

Preoperative occlusion of the renal artery was performed in a patient with a hypernephroma. This was accomplished with the use of wool coils.

A mylar sheath catheter was introduced percutaneously into the right femoral artery of a 45 year old male with a left hypernephroma. Through the mylar sheath a thinwall preformed, No. 7. French catheter of uniform inner diameter and non-tapered tip was passed with the assistance of a 0.045 inch guidewire. The left renal artery was selectively catheterized. Utilizing the procedure previously described, 4 coils were used to occlude the vessels supplying the majority of the neoplasm. The next day at the time of the left nephrectomy the surgeon commented about the ease of the operative procedure and the relative avascularity of the kidney and the neoplasm. The coils did not interfere with the ligation of the renal artery (Fig. 7).

DISCUSSION

An arterial bed can be obstructed from the periphery by occluding multiple small arteries or centrally by occluding a few larger arteries. The occlusion of small arteries by small emboli is more gradual and usually requires multiple injections. As the obstruction proceeds, the blood flow is gradually decreased. Rapid injection at that point may result in reflux of the emboli into territories at a distance from those intended. Central occlusion on the other hand requires larger and fewer emboli. This approach is more likely to result in collateral circulation to the vascular bed if given adequate time.

At M. D. Anderson Hospital 25 patients with a variety of malignant neoplasms were treated by transcatheter arterial emboliza-

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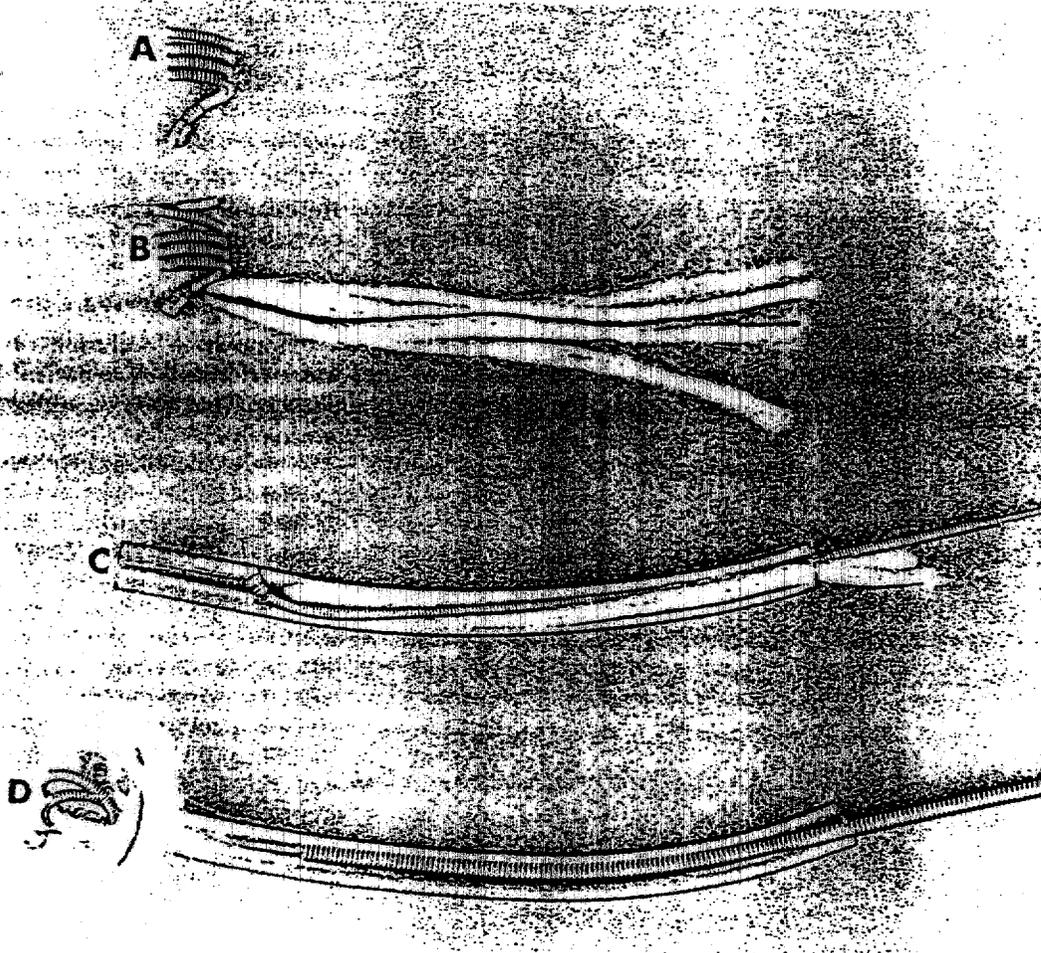


FIG. 4. Wool coil.

- A. The coiled wire segment, 3 cm. long.
- B. The coil with attached woolen strands 6 cm. long.
- C. The straightened wool coil within a clear plastic tube.
- D. The reformation of the wool coil, as it emerges from the catheter.

tion. One group of 7 patients with neoplasms was treated by arterial embolization to control bleeding which was refractory to more conservative management. These patients were poor surgical candidates. Successful treatment of the immediate problem of hemorrhage allowed time for definitive therapy for the primary disease. These included patients with lymphoma of the stomach, invasion of the sigmoid colon by an ovarian carcinoma, and choriocarcinoma of the uterus.

The majority of the patients, 18 of the 25, had renal carcinomas and occlusion of

the renal arteries was performed. In 9 of these patients occlusion was done preoperatively to reduce tumor vascularity. By decreasing arterial supply the venous drainage was markedly diminished, technically facilitating the nephrectomy. In the 9 patients with inoperable renal carcinoma, transcatheter arterial embolization was performed palliatively to reduce tumor bulk and to relieve symptoms of flank pain and hematuria.

Autologous clot, subcutaneous tissue, 5 mm. segments of stainless steel guide-wire, and Gel Foam were utilized as the

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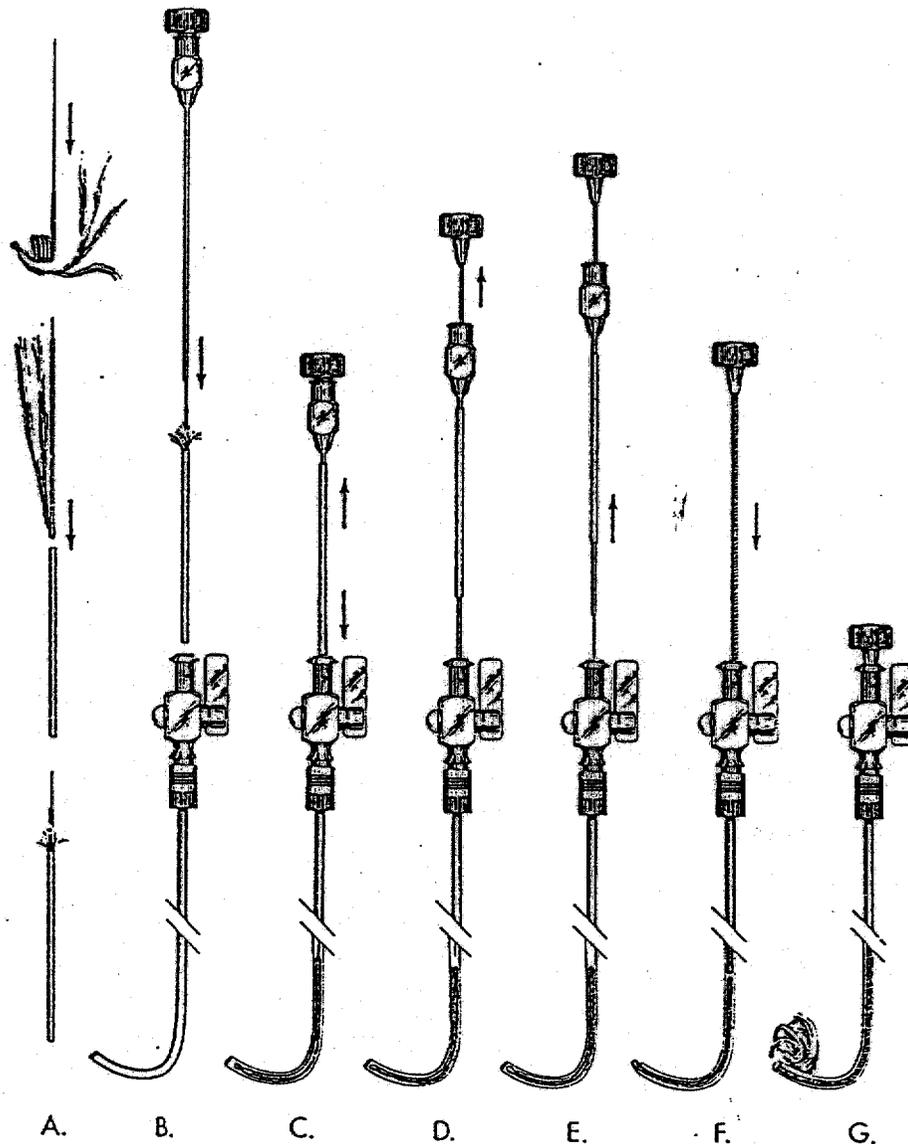


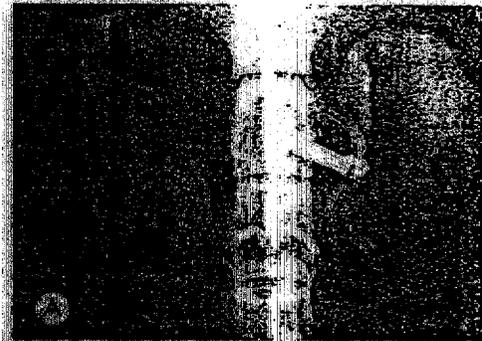
FIG. 5. Technique for embolization of wool coil.

embolic materials. At times a combination of these materials was used. Autologous clot was of temporary duration, lasting days prior to lysis. Subcutaneous tissues have the natural disadvantage of limited supply. The wire segments alone were ineffective in that they seemed to come into equilibrium with the blood stream after a thin coat, presumably fibrin, formed about the metal. Gel Foam was employed most frequently to occlude the small as well as the large

arteries. In a few of these patients a portion of the vascular supply was patent on follow-up arteriographic examination. All of these small particles run the risk of reflux from the embolized vessel as the vascular bed is occluded. This same problem would occur with the cotton tails. As the cotton tails are radiopaque, the site of the occlusion is obvious. The cotton portion of the embolus is effective as the nidus for occlusion.

FIG. 6. Embolization of wool coils.

- (A) Occlusion of a canine renal artery with a wool coil.
- (B) Specimen:
 - (1) Wool coil in a canine renal artery. The occlusion is at the proximal portion of the renal artery.
 - (2) Wool coil in the splenic artery specimen.



The wool coils readily occlude the larger arteries just beyond the tip of the catheter. The use of a Teflon catheter has the disadvantage associated with the more rigid and therefore more traumatic catheter material. In view of the non-tapered tip, the introduction of the catheter is accomplished through a Mylar sheath. The great advantage of this device is the ability to place the embolus at the specific site desired. The last two hypernephromas were embolized successfully with the use of wool coils.



FIG. 7. Embolization of renal carcinoma.

- A. Renal carcinoma of the left lower pole.
- B. Occlusion of the branches of the renal artery supplying the neoplasm.

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SUMMARY

Two mechanical devices for the purpose of occluding vessels are presented.

Cotton tails, small metallic segments with attached cotton threads, will effectively occlude small arteries of approximately 2 mm. in diameter.

Wool coils, 5 cm. segments of the outer portion of steel guidewires with attached wool strands, obstructed major vessels just beyond the tip of the catheter.

The use of these devices has been investigated in dogs and then applied clinically in the occlusion of renal arteries in patients with hypernephroma.

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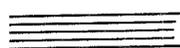
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