

## SECTION VII—Surgery of the Lower Colon and Rectum

### The Specificity of the Frei Test in Lymphopathia Venerea\*

By

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**T**HIS fascinating disease entity — lymphopathia venerea or lymphogranuloma inguinale—is of particular interest to us as proctologists by virtue of its interrelationship with various anorectal syndromes, especially stricture of the rectum and esthiomene which now are to be considered the most important sequelae of L.V. The subject is such a massive one and the literature so voluminous that in this brief space we will confine our remarks to but one phase of the disease, namely the specificity of the Frei reaction.

Many are prone to question the existence of such an affection as lymphopathia venerea as well as the value and reliability of the Frei test (42). We earnestly entreat our colleagues, however, to judge unbiasedly by the writings and experimentations of pioneer workers in this field of research. In a recent article by the Author (10) the ubiquity of this disease was cited in reports by 158 investigators representing twenty-one different countries of the world. Each of this number had confirmed the Frei test as a diagnostic aid. Surely the authenticity of the reports offered by such scientists as Levaditi, Hellerstrom, Wassen and Bensaude is not to be derogated. Is not the fact that in patients with a positive Frei test, experimental transmission of the unknown virus by inoculation with pus from an unopened bubo (106) and tissue from a rectal stricture (66, 86) through guinea pigs into monkeys, with the production of a typical meningoenephalitis which histologically corresponds to the lesion in the human, to be considered a conclusive proof? Further evidence may be cited in that the lesion so produced in the monkey, when prepared according to Frei's technic, gave a positive reaction when injected intradermally into the forearm of patients known to be affected with this disease. Leadrich states that "The experiments prove in a striking manner the specific value of Frei's intradermo-reaction and at the same time the incontestable etiologic role of Nicolas-Favre's disease in stenosing proctitis." Fischer (37) remarks "the intradermal test of Frei shows rather conclusively that stricture of the rectum and chronic granulomatous ulceration of the anus and vulva are due to the specific virus of L.V." Cole (20), who has observed a large number of these cases, mentions that the Frei test has

been of particular value in the diagnosis of the so called "anorectal syphiloma of Fournier." Bensaude (14), in describing the value of the Frei test remarks "The obscure and much discussed etiology of rectal stricture seems to be finally explained by the knowledge of lymphogranulomatosis inguinalis and which must now be added to the list of venereal diseases." Martin (75), who was the first to call our attention in Philadelphia to this interesting disease remarks, "the causative factor of stricture of the rectum, esthiomene and certain other anorectal infections which particularly appear to be an affection peculiar to the Negro race, has been we feel finally solved by the work of Nicolas, Durand, Favre and Frei." In an excellent article on the subject, Bloom (17) declares, "the problem of inflammatory stricture is inseparable from esthiomene." We believe, as others, that in a large percentage of cases this affection is part of L.V. A series recently tabulated by Hellerstrom (54), with their Frei reactions, is as follows:

#### ESTHIOMENE

| Authors                     | Number of<br>Cases | Frei<br>Positive |
|-----------------------------|--------------------|------------------|
| Frei and Koppel             | 12                 | 12               |
| Kleeberg                    | 14                 | 14               |
| Bensaude and Lambling       | 21                 | 19               |
| Barthels and Biberstein     | 7                  | 7                |
| Jersild                     | 12                 | 12 (11)          |
| Gregorio                    | 27                 | 27               |
| Gay Prieto                  | 21                 | 19               |
| Ravant                      | 19                 | 19               |
| Nicolau                     | 14                 | 14               |
| Lohe                        | 10                 | 10               |
| Hurwitz                     | 8 - 12             | 8 - 12           |
| DeWolf                      | 7                  | 7                |
| Cedercreutz                 | 5                  | 5                |
| Peterson                    | 6                  | 6                |
| Kitchevatz                  | 3                  | 3                |
| Fischer and Schmidt-LaBaume | 5                  | 5                |
| A. W. Meyer                 | 4                  | 4                |
| Lutz                        | 4                  | 4                |
| H. Strauss                  | 3                  | 2                |
| Langer and Engel            | 2                  | 2                |
| Strombeck                   | 1                  | 1                |
| Peyri                       | 1                  | 1                |

Total

206 - 210    201 - 205

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\*Read at the thirty-sixth annual meeting of the American Proctologic Society, Atlantic City, June 10th and 11th, 1935.  
Submitted August 8, 1935.

It is interesting to note that Ravaut, Levaditi, and Cachera (86) upon inoculating a guinea pig with ulcerated growths from the anus of a patient with a positive Frei test, observed that a typical lesion of L.V. was produced by transmitting the disease directly to monkeys. Later Meyer and Rosenfeld (79) injected the excised tissue from an esthiomene patient into a guinea pig which subsequently showed a process similar to that of L.V. Loehe (71) and Lutz (73) not only support the interrelationship between esthiomene and L.V. but state that this evidence must be considered conclusive. In four instances we have excised a portion of the esthiomene tissue, which when prepared according to Frei's technic, gave positive intracutaneous reactions in known cases of L.V. Well worth mentioning is the experiment of Nicolas, Favre and Charpy (81) who obtained a positive Frei test in a known L.V. patient with an antigen prepared from the pus of an anorectal fistula. This we have confirmed in a series of six cases.

Many workers in this field have referred to the Frei test as specific for this disease. (99, 87, 9, 52, 55, 33, 92, 85, 97, 18, 84, 82, 65, 64, 63, 62, 59, 47, 45, 61, 56, 38, 40, 35, 23, 7, 8, 11, 15, 13, 68, 31, 32, 43, 108, 104, 36, 76, 4, 5, 70, 103, 2, 19, 110, 112).

A few with their percentage of positive reactions are tabulated as follows:

| Author                               | Bib. | Per-centage | Service | Path-ology Rectal      | Genital |
|--------------------------------------|------|-------------|---------|------------------------|---------|
| Curth, W. (28)                       |      | 100%        | 77      | 50-S.                  | 27      |
| Vander Veer (102)                    |      | 100%        | 46      | 21-S.                  | 26      |
| Hellerstrom, S. (53)                 |      | 100%        | 47      | 0                      | 47      |
| *Hill, M. (58)                       |      | 100%        | 34      | 34-S.                  | 0       |
| Dalton 1934 (29)                     |      | 100%        | 24      | 0                      | 24      |
| Dalton 1935 (30)                     |      | 100%        | 200 ?   | 15                     | 185     |
| Grace, A. (46)                       |      | 100%        | 40      | 20-S.                  | 20      |
| Cole, DeWolf, Van Cleve (20)         |      | 100%        | 52      | 13-S.                  | 37      |
| Lehman, C. F. and Pipkin, J. L. (69) |      | 100%        | 22      | 3-S.                   | 17      |
| Cole, H. 1935 (21)                   |      | 100%        | 100-200 | 2-E.                   | ?       |
| DeWolf, H. 1935 (34)                 |      | 100%        | 3       | 3-S.                   | 0       |
| Van Cleve, J. 1935 (101)             |      | 100%        | 5       | 0                      | 5       |
| Streicher, M. (97)                   |      | 100%        | 19      | 11-S.<br>5-F.          | 3       |
| *Marino, M. (74)                     |      | 100%        | 4       | 4                      | 0       |
| *Hayden, E. P. (50)                  |      | ?           | 20      | ?                      | ?       |
| Grossman, S. (48)                    |      | 100%        | 5       | 4-S.<br>1-A.F.         | 0       |
| *Alley, R. (1)                       |      | 100%        | 20      | 20-S.                  | 0       |
| Burney, L. E. (111)                  |      | 100%        | 10      | -                      | -       |
| Howard, M. and Strauss, M (60)       |      | 100%        | 16      | 5-S.<br>1-A.F.<br>1-C. | 9       |
| Wien, M. (107)                       |      | 100%        | 16      | ?                      | ?       |
| Bloom, D. (17)                       |      | 100%        | 7       | 7-S.                   | 0       |
| Coutts, W. 1934 (24)                 |      | 100%        | 7       | 2-S.<br>2-A.F.         | ?       |
| Wang, L. and Shen, J. (105)          |      | 100%        | 5       | 2-S.                   | 3       |
| *Templeton and Smith, D. (100)       |      | 100%        | 1       | 1-S.                   | 0       |
| *Martin, C. F. and Bacon, H. E. (78) |      | 96.7%       | 155     | 75-S.<br>56-A.F.       | 24      |
| Sulzberger, M. (98)                  |      | 96.3%       | 27      | 6-S.                   | 21      |
| Strauss, H. (94)                     |      | 96%         | 72      | ?                      | ?       |
| Bensaude, R. (12)                    |      | 90%         | 27      | 24-S.                  | 3 ?     |
| Lee, H. and Staley, R. (67)          |      | 87%         | 16      | 14-S.                  | 2 ?     |
| G. Prieto (83)                       |      | 86%         | ?       | ?                      | ?       |
| Stillman, A. (113)                   |      | 83%         | 6       | 6-S.                   | 0       |
| Corcoran, M. (22)                    |      | 75%         | 4       | 3-?                    | ?       |
| Coutts, W. 1933 (27)                 |      | 68.7%       | 32      | ?                      | ?       |
| *Hayes, H. and Burr, H. (51)         |      | 60.4%       | 106     | 106-S.                 | 0       |

S.—Stricture  
A.F.—Abscess and Fistula  
\*—Members of A.P.S.  
C.—Condylomata  
E.—Esthiomene

In order to substantiate the intracutaneous test of Frei, Coutts and Bianchi (26) studied the Bordet-Gengou complement reaction in relation to different

syndromes of L.V. by using an antigen prepared from the lymph nodes as a receptor. After months of research these authors (25) report that this complement fixation is specific for L.V. and supports Frei's intradermal test. Another experiment worthy of mention is that by Strauss (93) who found that where the Frei test is strong enough to cause vesicle formation, the content of this vesicle is capable of producing reaction similar to that of the Frei in patients with L.V. In our series of 155 cases, 150 gave a positive Frei test, or 96.7%. Thirty-six different antigens were used, 25 from our cases and the others sent to us by Van Cleve, Hill, Hayden, Strauss, McKenney, Jelks and Reimann in the U. S. and Almanza in Bogota, Hellerstrom in Stockholm, Levaditi in Paris, McDonagh and Stannue in London, and Coutts in Chile. Each test was verified always using a second antigen, usually a third and frequently a fourth. Through the courtesy of Drs. Coca and Roberts, we have utilized the saline suspension of mouse brain prepared by the Lederle Laboratories and find that it compares favorably with our own antigen and those received from others. In order to evaluate the test properly a control antigen obtained from the normal gland of patients not affected with L.V. was used as suggested by Martin (77). In some instances a sterile suspension of leukocytes was injected, while in other cases a control of 0.25 per cent phenol in normal saline solution, as mentioned by Wang (105), was utilized. All controls were negative.

TOTAL NUMBER OF CASES SHOWING POSITIVE FREI TEST—150

SEX  
Females ..... 85  
Males ..... 65

RACE  
Colored ..... 118  
White ..... 31  
Chinese ..... 1

FEMALES  
Colored ..... 71  
White ..... 14

MALES  
Colored ..... 47  
White ..... 17  
Chinese ..... 1

AGE  
FEMALES  
17-29 ..... 38  
30-39 ..... 27  
40-49 ..... 15  
50-61 ..... 5  
Total ..... 85  
MALES  
14-29 ..... 27  
30-39 ..... 16  
40-49 ..... 12  
50-59 ..... 7  
60-73 ..... 3

PATHOLOGY:

FEMALE  
Stricture (alone) ..... 59  
Stricture and esthiomene... 4  
Esthiomene (alone) ..... 2  
Abscess and Fistulae..... 12  
(multiple)  
Post-anal infection ..... 4  
Ulcerative procto-colitis... 1  
Anal stenosis ..... 3

Total ..... 85

**PATHOLOGY:**

| MALE                      |    |
|---------------------------|----|
| Anorectal stricture ..... | 7  |
| Abscess and Fistula.....  | 22 |
| Anal stenosis .....       | 8  |
| Post-anal infection ..... | 4  |
| Inguinal adenitis .....   | 24 |
| Unilateral .....          | 13 |
| Bilateral .....           | 11 |
| Total                     | 65 |

In an attempt to rule out various diseases such as syphilis, gonorrhoea, tuberculosis, and ulcus molle, which may cause or at least have been considered the etiologic factors in L.V., certain laboratory tests were performed. Of the 150 cases herein reported, the blood Wassermann and Kahn, and in some instances the Kolmer and Eagle, were taken in 97 instances. At the suggestion of Dr. Edwin Gault a small series was given provocative doses of neoarsphenamine. Seventeen patients showing a negative Wassermann reaction were injected with 3 mg. after which another test was taken. In each case the report was negative.

| REACTION       | Number      |
|----------------|-------------|
| Negative ..... | 71          |
| Positive       |             |
| / 4 .....      | 22          |
| / 3 .....      | 3           |
| / 2 .....      | 0           |
| / 1 .....      | 1           |
|                | 26 or 26.8% |
| Total          | 97          |

We wish to mention that in our series of 155 cases, 150 of which showed a positive Frei test, three of the five remaining showed a positive Wassermann reaction. During the institution of antiluetic treatment and even after the completion of the course, we failed repeatedly to obtain a positive Frei test. Apparently there exists a reciprocal immunologic reaction between syphilis and L.V. which thus far has not been explained, for it has been observed (39, 16) that in the presence of a recent or an active syphilitic process the Frei test may be rendered temporarily negative.

Smears for the gonococcus were taken in a limited number of cases. Two smears were taken and each stained by the Gram technic. The results were noted as follows:

|                          |            |
|--------------------------|------------|
| Rectal Smears for G. C.  |            |
| Negative .....           | 28         |
| Positive .....           | 6 or 17.6% |
| Total                    | 34         |
| Vaginal Smears for G. C. |            |
| Negative .....           | 41         |
| Positive .....           | 13 or 24%  |
| Total                    | 54         |

Reenstierna Test for chancroidal infection (87, 88, 89). Through the courtesy of Almanza of Bogota and Reenstierna of Stockholm, we obtained a supply of Dmelcos vaccine (suspension of *B. cucrey* and streptococcus) which is considered specific for chancroids (3, 57, 109) termed on the Continent *ulcus molle*. Forty-one cases showing a positive Frei test were injected intradermally with 1/10 c.c. of the Dmelcos vaccine. Thirty-eight gave a negative reaction. Of the three showing a positive Reenstierna test, two of this number presented clinical evidence of chancroidal infection.

| NUMBER         |    |
|----------------|----|
| Negative ..... | 38 |
| Positive ..... | 3  |
| Total          | 41 |

In one instance we attempted to transmit the Ducrey organisms to the forearm of the patient after scarification but without success.

*Tuberculosis.* To determine the presence or absence of tuberculosis is a most perplexing problem especially when applied to the use of tuberculin. Either it is inert in a large percentage of instances or there is considerable chance of falsely interpreting many reactions as positive. The new standard tuberculin termed "Purified Protein Derivative" (P.P.D), prepared by Seibert (90, 91) and adopted by the National Tuberculosis Association, is considered of greater value than O.T. (49, 72, 80) in that it is free of salts and non-specific proteins and that its potency is reproducible (6). With the assistance of Dr. Gault, Pathologist to the Temple University, School of Medicine, forty-five patients in our series were tested intradermally with P.P.D., using the first dilution (0.00002 mg.). Their reactions were read and measured in 48 hours. The second dilution (0.005 mg.) was injected in cases that were negative to the first. The results were as follows:

| Reaction   | Number |
|--|--------|
| Negative   | 33     |
| Positive 1 reaction shows area of swelling measuring 5 to 10 mm. in diameter ..... | 1      |
| 2 reaction shows area of swelling measuring 10 to 22 mm. in diameter .....         | 5      |
| 3 reaction shows area of swelling exceeding 20 mm. in diameter ..                  | 3      |
| 4 reaction shows area of swelling and definite necrosis.....                       | 3      |
| Total  | 45     |

Of the 12 cases showing a positive P.P.D. test, five presented clinical and histologic evidence of tuberculosis: pulmonary 2, fistula 1, nodule 1 and anal skin 1. All, however, showed a positive Frei reaction.

In an effort to determine the percentage of positive Frei tests in various affections other than L.V., we solicited the services of our colleagues in allied clinics. Negative Frei tests were obtained in the following cases:

## FREI TEST CONTROLS

|                                     | Number<br>of Cases |
|-------------------------------------|--------------------|
| Healthy                             | 44                 |
| Colitis, various forms              | 21                 |
| Syphilis, — skin                    | 4                  |
| Stomach ?                           | 1                  |
| Tuberculosis, — intestinal          | 3                  |
| pulmonary                           | 12                 |
| Gonorrheal urethritis and vaginitis | 9                  |
| Cholecystitis                       | 9                  |
| Gastric or duodenal ulcer           | 7                  |
| Carcinoma larynx                    | 1                  |
| Carcinoma prostate                  | 4                  |
| Carcinoma breast                    | 1                  |
| Carcinoma stomach                   | 5                  |
| Lipoma                              | 3                  |
| Actinomycosis                       | 1                  |
| Hodgkin's disease                   | 1                  |
| Thyroid disease                     | 3                  |
| Fractures                           | 4                  |
| Pyelitis                            | 4                  |
| Influenzal conditions               | 14                 |

## RECTAL

|                               |    |
|-------------------------------|----|
| Carcinoma, rectum             | 9  |
| Benign adenoma                | 3  |
| Post-anal ulcer and infection | 12 |
| Hemorrhoids                   | 47 |

|                      |    |
|----------------------|----|
| Abscess and Fistulae | 34 |
| Tuberculous fistulae | 2  |
| Pruritus ani         | 6  |

Total 264

In a recent communication to C. F. Martin, Silvers reported a series of 100 control cases from the Atlantic City Hospital in which all gave a negative Frei test.

## CONCLUSION

By repeated testings the Frei test has proven specific and has assisted in the recognition of the heretofore unaccepted therapy of L.V. Over a period of two years we have observed these patients and their Frei reactions in various stages of the disease, and feel that in the presence of clinical evidence one negative test should not be considered as confirmatory that the process is not one of L.V. To a large degree, incorrect readings may be obviated by careful selection of the tissue used, strict adherence to the preparation and preservation of the antigen, its method of administration and time of reading.

We consider the Frei test to be of utmost value in the diagnosis of L.V. judging from our total series of 155 cases bearing a positive percentage of 96.7 that clinically and pathologically presented manifestations of this disease, but we do concur with Guy del Vivo (44) that further and more conclusive evidence should be sought as to its etiology.

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## ABSTRACTS

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*Pectenosis and Minor Maladies of the Anal Region.*  
S., G. and O., Vol. LIX, No. 5, Nov., 1934, pp. 806-809.

The author wishes to call attention to the importance of the variety of lesions found in the anal canal, and to record some personal observations as to their clinical findings and treatment. A consideration of the anatomy of the part is important. Four landmarks are recognized, namely: (1) the ano cutaneous line which marks the lower end of the intestinal tract; no hair follicles are seen cephalad to this line, (2) the white line of Hilton which lies 1.5 centimeters above the anocutaneous line. It is from six to nine millimeters in width, and, during life, is blue in color, (3) the pectinate line is represented by the lower margins of the sinuses and columns of Morgagni, (4) the ano rectal line is 1.5 centimeters above the pectinate line; it can be accurately identified only with the aid of the microscope. The pectinate line is the important area as it is here that the blood, lymphatic and nerve supply divide. When the anal orifice is closed, the pecten forms the central part

of the floor of the rectum, and it is reasonable to suppose that it should be the seat of special organs whose function it is to regulate the action of the sphincter muscles. Any disturbance of the equilibrium of the sphincters leads to chronic passive congestion, which in turn leads to round cell infiltration, fibrosis, and the production of a condition termed pectenosis. The fibrous deposit, which varies in breadth and thickness according to its duration, encircles the canal, and was called "the pecten band" by Miles in 1918. Passive congestion may result from many causes; e. g.; haemorrhoids, contusions or lacerations of the canal, irritating liquid stools, etc. The resulting pectenosis persists and becomes more marked, aggravating the primary condition until it is corrected. During the last year and a half the author has operated on 83 patients whose lesions could be explained by the presence of pectenosis and a pecten band. In most cases where the pecten band is well defined simple incision of it affords complete relief. The author warns against the practice of divulsion as it is always dangerous.

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