

STREPTOCOCCAL ENZYMATIC DEBRIDEMENT*

WILLIAM S. TILLET, M.D., SOL SHERRY, M.D., L. R. CHRISTENSEN, PH.D.†
ALAN J. JOHNSON, M.D., AND GEORGE HAZLEHURST, M.D.

NEW YORK, N. Y.

FROM THE DEPARTMENT OF MEDICINE, NEW YORK UNIVERSITY COLLEGE OF MEDICINE
AND THE THIRD MEDICAL DIVISION, BELLEVUE HOSPITAL, NEW YORK

IT HAS BEEN RECENTLY demonstrated that concentrates derived from cultures of hemolytic streptococci containing streptokinase (streptococcal fibrinolysin) and streptodornase (streptococcal desoxyribose nuclease) can be introduced locally into the thoracic cavity of patients in sufficient quantities to effect substantial and rapid enzymatic changes without causing serious untoward reactions.¹

It is the purpose of this report, which is an extension of previous ones on several detailed aspects of this subject,²⁻⁵ to describe the well-defined clinical therapeutic results that have been obtained by the treatment, through local injection of the lysing enzymes into selected groups of patients.

The patients who have been treated suffered from diseases characterized by the undesirable presence of fibrinous or purulent exudations. The categories into which they so far fall are as follows:

1. Loculated, post-pneumonectomy hemothorax.
2. Traumatic hemothorax.
3. Sterile loculated empyema.
4. Bacterial empyema.
5. Other local infections (osteomyelitis, paranasal sinusitis, etc.).
6. Miscellaneous chronic ulcerative lesions.

Detailed data and comprehensive analyses of each of the groups is planned for subsequent publications. In order, however, to illustrate the nature of the results that are being obtained, the descriptions which follow are limited to an example of each of the types of patients that have been treated. Since photographs demonstrate the results more clearly and objectively than verbal descriptions, each of the cases is presented with accompanying figures and the text has been reduced to the minimum.

The partially purified streptococcal concentrates employed have been prepared according to methods originally developed by one of us (L. R. C.).^{4,5}

Both streptokinase (to be, for brevity's sake, referred to as SK) and streptodornase (to be referred to as SD) were present in the partially purified

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‡ A considerable amount of the preparations was supplied by Lederle and Co.

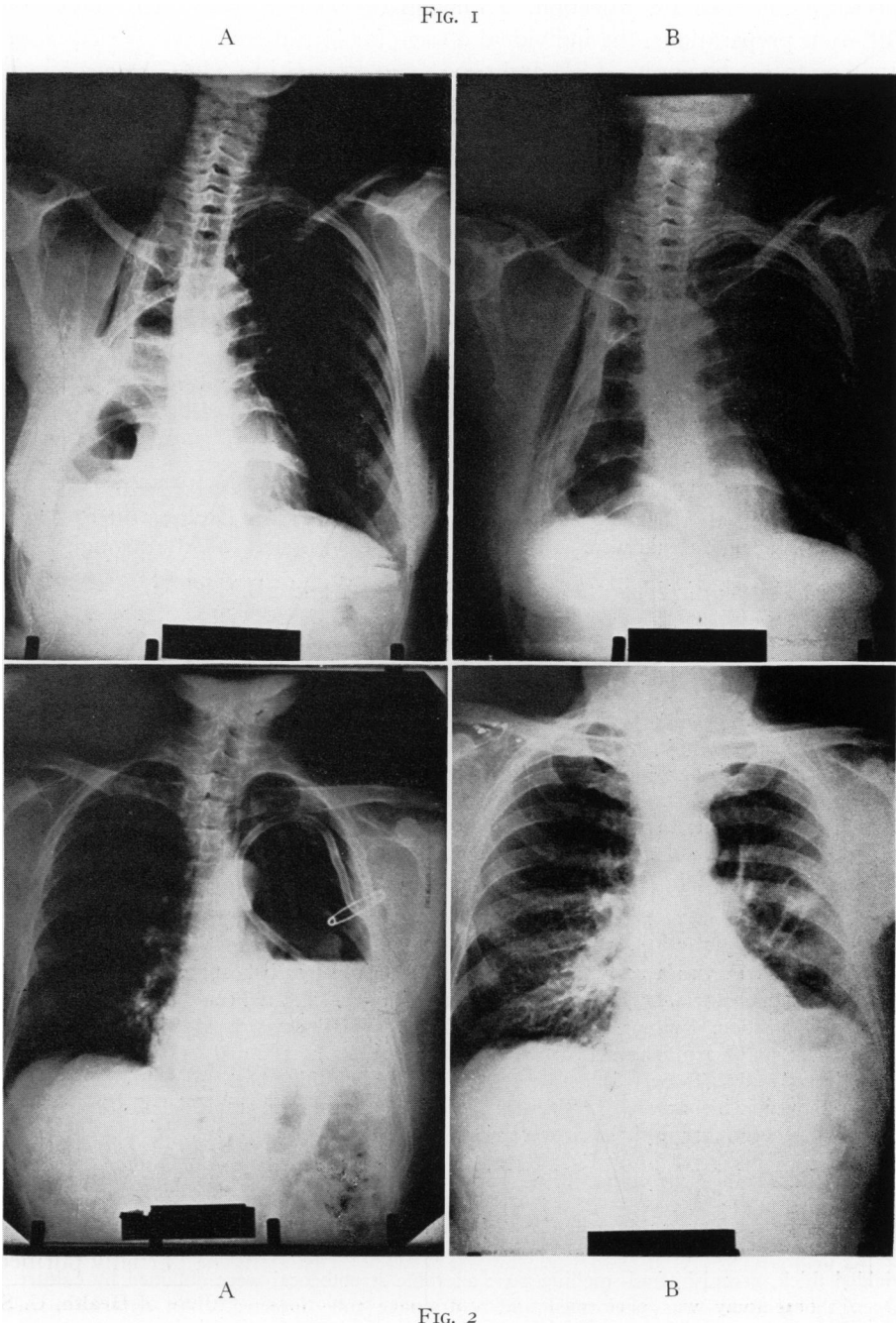


FIG. 1.—Patient A. L. Loculated, postoperative, hemothorax. (A) Before treatment. Loculated areas evident. (B) Twenty-four hours after treatment. 650 cc. of fluid removed by aspiration.

FIG. 2.—Patient H. F. Traumatic hemothorax. (A) Tube below level of fluid but drainage ineffective. Complete collapse of lung present. (B) Roentgen ray taken at time of discharge from hospital, 55 days after beginning of treatment.

preparations used for injection. Although the quantities of each varied in different preparations, the individual dosage for intrathoracic use varied from 100,000 to 400,000 units of SK and 5000 to 40,000 units of SD. The combined units of each were contained in 2 to 10 cc. of physiologic salt solution. Where the areas of disease were smaller (such as in the cases listed under headings 5 and 6) the unit content of the material introduced was also smaller but treatments were repeated over several days or weeks.

I. *Loculated Post-Pneumonectomy Hemothorax.* (See Figs. 1A and 1B.)

The results obtained in the treatment of one of the patients of this group has been previously reported.¹ The description of an additional patient is as follows:

Patient A. L. was a 35-year-old white female. Pulmonary tuberculosis was first noted in 1947. Induction of pneumothorax was subsequently followed by development of pleural effusion. Thoracoplasty was performed in August, 1948. Right pneumonectomy was performed in October, 1948. Postoperatively multiple loculations of fluid were collected with scant yield from aspiration at any site. Seventeen days later 200,000 units of SK (with minimal SD) were injected into each of two areas. During next 24 hours 650 cc. of sanguinous fluid were easily removed.

II. *Post-Traumatic Hemothorax.* (See Figs. 2A and 2B.)

Patient H. F. was a 52-year-old white male. Multiple fractured ribs were sustained, with development of pneumo-hemo-thorax. Blood could not be adequately drained. After 3 weeks, closed thoracotomy was performed. However, even with tube in proper position, drainage was meagre and complete collapse of lung persisted. Three days later 100,000 units of SK (with minimal SD) was introduced through the tube and a second dose injected intercostally. The tube was clamped off to retain SK. Three hours later clamp removed and suction applied. Several hundred cc. (not measured) of fluid were removed by aspiration within a few hours. The lung promptly expanded. Subsequently, when drainage became minimum, the tube was removed. Recovery was uneventful.

III. *Loculated, Post Pneumonic, Empyema, Sterile.* (See Figs. 3A and 3B.)

Patient T. P. was a 40-year-old white male. On nineteenth hospital day of pneumococcal lobar pneumonia, only 50 cc. of thick, greenish purulent fluid could be removed from chest by aspiration. Cultures were sterile. Pleural loculations were evident by roentgenogram. Ten cc. of a preparation containing 100,000 units of SK and 25,000 units of SD were introduced. Twenty-four hours later 465 cc. of thin, blood-tinged, cloudy fluid was removed with ease. Temperature fell to normal and rapid clinical recovery occurred. No further aspirations were necessary.

IV.-1. *Bacterial Empyema.* (See Figs. 4A and 4B.)

Patient W. K. was a 65-year-old white male. After a month of cough and thoracic pain he was admitted to hospital. Evidence of pleural effusion was present. Thoracentesis yielded thick, greenish, foul-smelling pus; anaerobic streptococci were obtained by culture. Open thoracotomy was performed and a drainage tube inserted. An anterior paramediastinal pocket remained undrained. Additional foul-smelling pus was aspirated by direct anterior intercostal approach and 3 cc. of a solution containing 100,000 units of SK and 5400 units of SD, together with 100,000 units of penicillin, was introduced into the pocket. During the ensuing 24 hours about 75 cc. of exudate was aspirated directly. There was some increased drainage through the tube. Recovery was rapid and uneventful.

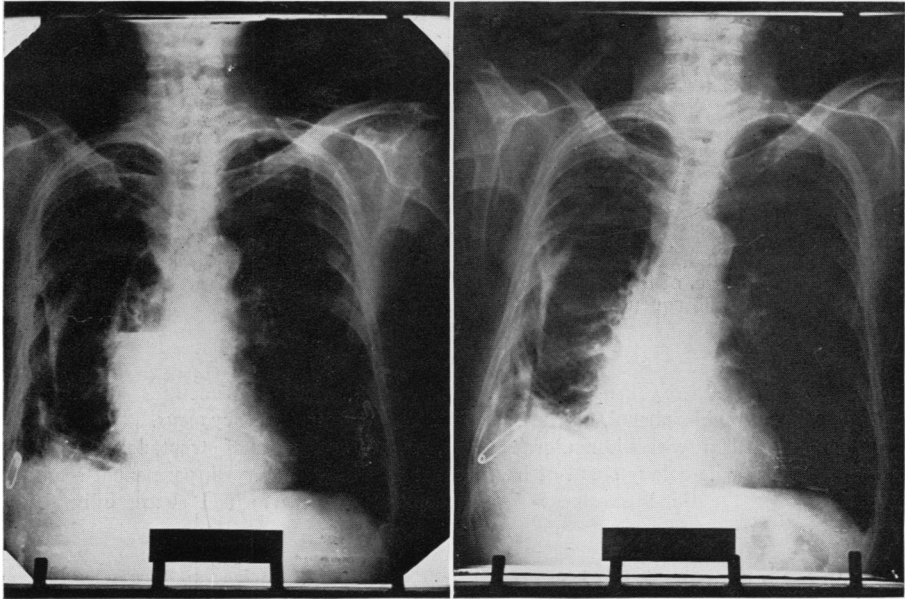
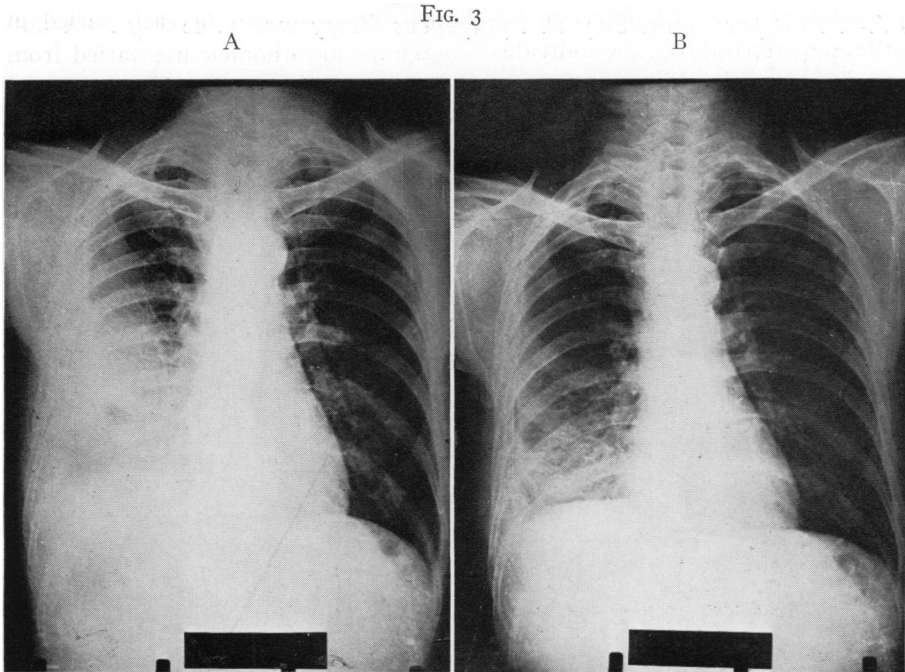


FIG. 3.—Patient *T. P.* Postpneumonic, loculated, empyema. (A) Before treatment. Loculated areas present. (B) Twenty-four hours after treatment 465 cc. of fluid removed by aspiration.

FIG. 4.—Patient *W. K.* Bacterial Emphyema (*Aerobic Streptococcus*). (A) Right para-mediastinal pocket of loculated pus with fluid level. (B) Twenty-four hours after treatment, pocket disappeared and did not reform.

IV.-2. *Post-pneumonectomy B. Pyocyaneus Empyema.* (See Figs. 5A and 5B.)

Patient J. H. was a 63-year-old white male. Pneumonectomy, which had been preceded by pneumonotomy 15 months previously, was performed for lung abscess. *B. pyocyaneus*, which had been originally present in the abscess, was also present post-operatively, in the thoracic exudate which loculated. 200,000 units of SK (with minimal SD) was injected; 24 hours later 1100 cc. of sanguinous fluid was aspirated. Loculations

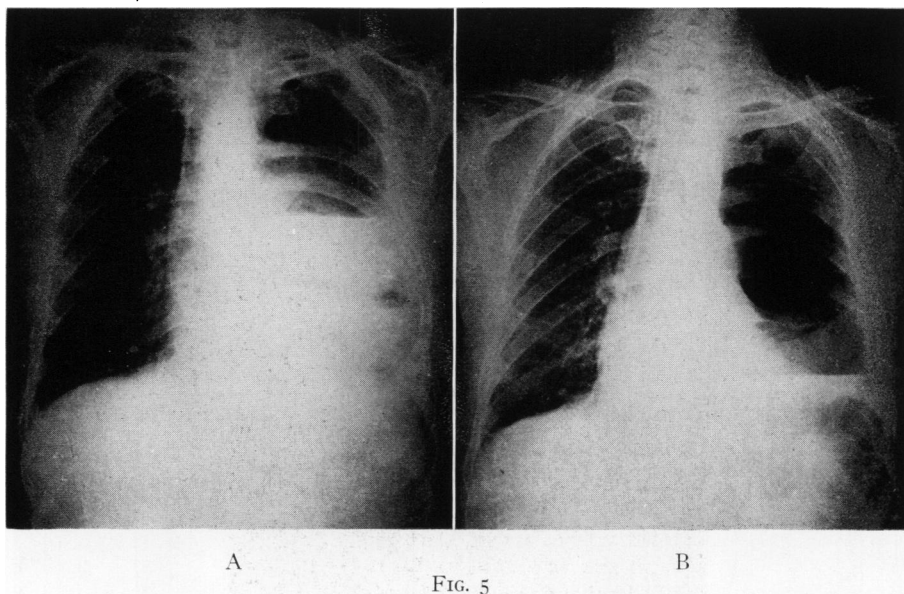


FIG. 5.—*Patient J. H. Bacterial Empyema, Post-pneumonectomy (B. pyocyaneus).* (A) Fluid levels and loculations present. (B) Twenty-four hours after treatment, 1100 cc. of fluid were removed by aspiration. Shadow over lower portion of left thorax subsequently disappeared.

disappeared but *B. pyocyaneus* remained. Local installations of penicillin, sulfadiazine, streptomycin, parachlorophenol, and urethane failed to affect *B. pyocyaneus*.

The patient then received on alternate days, 7000 to 9000 units of streptodornase (with minimum SK). The colony count of bacteria progressively decreased, permanent sterility occurring after the third treatment. Thoracoplasty was performed successfully three weeks later.

The results obtained in this patient deserve special comment. Since *B. pyocyaneus* does not have primary pathogenic properties for man, its presence in infection is usually that of a secondary invader into areas of disease where damaged tissue or exudate previously existed. In patient J. H., therefore, the removal of the exudate and debris through the application of *streptococcal enzymatic debridement* permitted the antibacterial factors of humoral and cellular resistance of the patient to destroy the organisms. This finding,

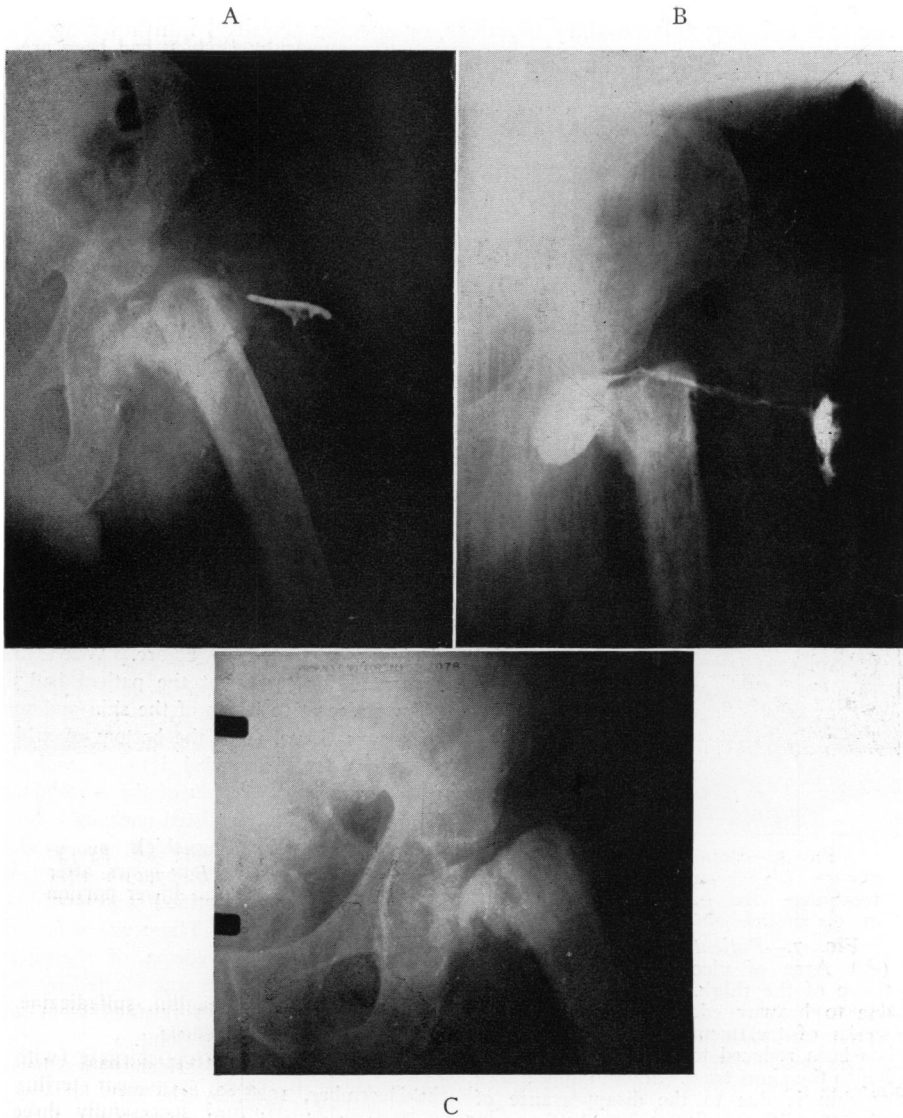


FIG. 6

FIG. 6.—*Patient P. C.* (A) Effort to introduce Diodrast into sinus tract was ineffectual. The areas of acetabulum, ilium and lateral surface of upper femur appear mottled. (B) After the second treatment, Diodrast was introduced, the shadow of which indicates sinus tract and location of inner pocket of infection in the region of the acetabulum. (C) Treatment terminated; no Diodrast present. The mottling, presumably caused by exudative debris, is considerably reduced. This roentgenogram is interpreted as revealing a part of head of femur fixed in acetabulum, and new bone formation from the inner surface of top of misplaced femur; confirmed at operation.

together with similar ones noted in other patients of our series, indicates that special principles are operative through which either natural immunity against bacteria existing as secondary invaders, or specific acquired immunity against primary pathogenic strains, are capable of gaining access to and destroying the organisms present in chronic infections, following the enzymatic cleaning of the tissues.



FIG. 7

FIG. 7.—*Patient P. C. (Continued)*
(A) Area of ulcerated wound of soft tissue of the thigh. Note wrinkled skin due to brawny edema. (B) After two weeks of treatment the area of wound has been reduced to a small funnel leading to the sinus tract. Smooth appearance of skin is due to the disappearance of edema.

given daily injections of 20,000 units of SK and 4000 units of SD for approximately 10 days.

The effects beginning within 48 hours were as follows: First, the amount of exudate increased, and it was noticeably thinner. The odor disappeared. The brawny edema lessened and finally disappeared. The pain lessened. The catheter was now readily inserted into the acetabular area and the cavity outlined by roentgen rays taken following the introduction of diodrast.

The oblong superficial wound progressively decreased in size, leaving only the sinus tract at the upper angle of the wound.

V.-I. *Osteomyelitis with Chronic Draining Sinus Tract and Ulceration of Skin and Soft Tissues.* (See Figs. 6A, 6B, 6C, 7A and 7B.)

Patient P. C. was a 50-year-old white male. Intertrochanteric fracture was sustained in March, 1947. A Smith-Peterson nail was inserted; in January, 1948, it was removed. A sinus developed in the lateral aspect of the thigh which drained foul purulent material. In June, 1948, part of the greater trochanter was removed, but sinus drainage continued as before. When first presented for treatment the patient had an oblong ulcerative lesion of the skin and subcutaneous tissue, from the bottom of which the sinus tract extended into an undetermined area in the region of the acetabulum. This situation had persisted unchanged for 6 months. Foul smelling thick pus exuded. On culture *B. proteus*, *B. pyocyaneus*, *Staph. albus*, and other unidentified saprophytic organisms were present. There was a brawny indurated non-pitting edema of the upper half of the thigh. Pain was elicited by palpation, and severe pain resulted from any effort to manipulate the joint.

Lysing enzymatic debridement was begun in December, 1948, by the introduction of concentrate deep into the sinus tract through a small plastic catheter. The patient was

FIG. 8

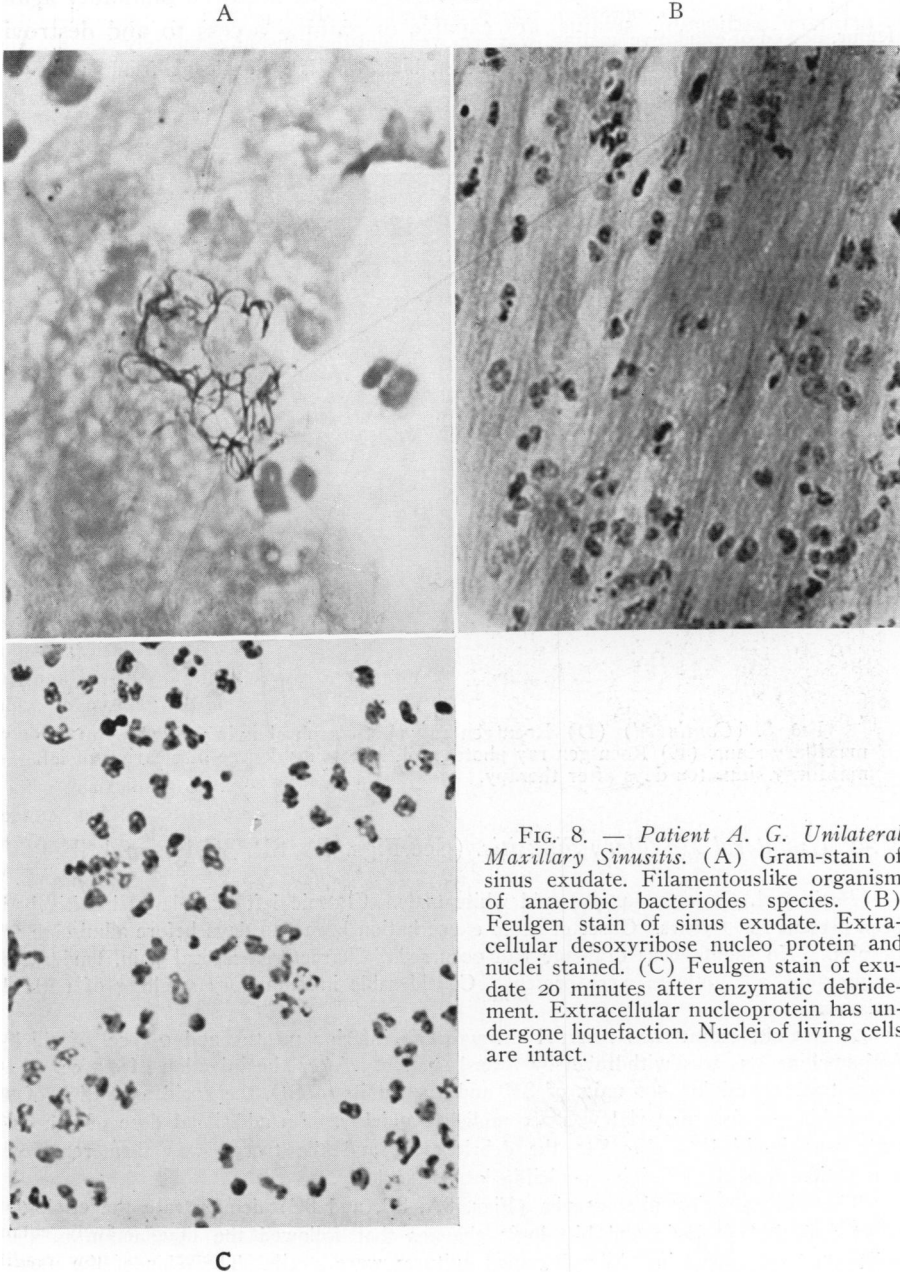


FIG. 8. — Patient A. G. Unilateral Maxillary Sinusitis. (A) Gram-stain of sinus exudate. Filamentouslike organism of anaerobic bacterioides species. (B) Feulgen stain of sinus exudate. Extracellular desoxyribose nucleoprotein and nuclei stained. (C) Feulgen stain of exudate 20 minutes after enzymatic debridement. Extracellular nucleoprotein has undergone liquefaction. Nuclei of living cells are intact.

After 5 weeks of additional intermittent therapy it was possible to demonstrate a piece of the head of the femur as a sequestrum in the acetabulum. The pain completely disappeared and the patient could sit up in bed and also extend his foot to the floor.

In February, 1949, operation was performed, the dead portion of the head of the femur, devoid of exudative coating, was removed, and the incision completely closed. The patient at present continues in a plaster cast, but there is no drainage from the site of the original sinus tract.

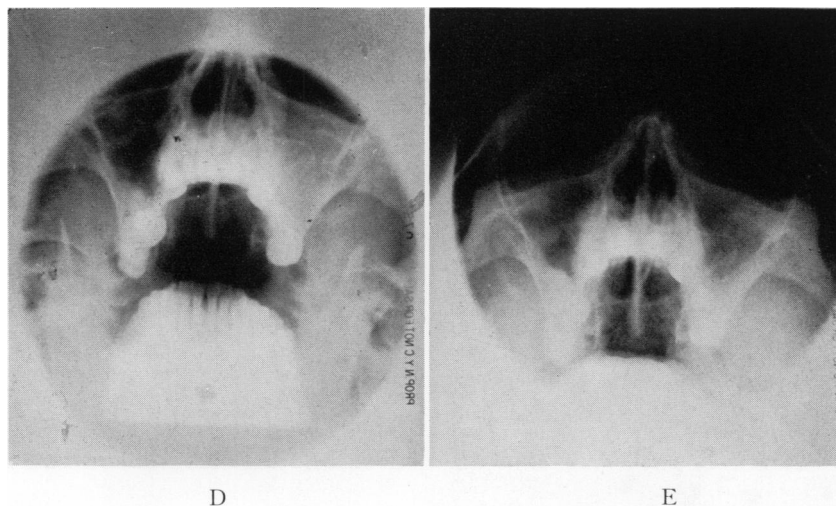


FIG. 8

FIG. 8. (*Continued*) (D) Roentgen ray photograph showing clouding of left maxillary sinus. (E) Roentgen ray photograph indicating degree of clearing of left maxillary sinus ten days after therapy.

V.-2. *Unilateral Maxillary Sinusitis.* (See Figs. 8A, 8B, 8C, 8D and 8E.)

Patient A. G. was a 42-year-old white male. Chronic left maxillary sinusitis had been present for 3 years. Onset of acute exacerbation began 10 days before admission to hospital. No spontaneous drainage had occurred. Characteristic local pain, tenderness on pressure, and fullness were present. Considerable inflammatory swelling of natural ostia was present.

A straight trocar was inserted through the inferior meatus and 0.5 cc. of thick, foul-smelling pus was withdrawn by forced suction. After the injection of 0.5 cc. of a concentrate containing 500 units of SK and 1000 units of SD, the rapid aspiration of 5 cc. of thin purulent material was accomplished quickly. An additional dose of concentrate was instilled to complete the debridement and the trocar was then removed. The patient was also receiving penicillin intramuscularly.

The accompanying photographs (Figs. 8A, 8B, and 8C) demonstrate the etiologic agent and the cytologic and histologic changes that followed the liquefaction of the sedimented nucleoprotein. All subsequent cultures were sterile. The odor of the purulent exudate disappeared.

The patient obtained considerable relief from symptoms. The edema of the natural ostia subsided and drainage through it occurred spontaneously. The patient appeared well 8 weeks after the debridement. (See Figs. 8D, and 8E.)

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FIG. 9.—(A) Appearance of ulcerative lesion before treatment. (B) Appearance after ten days of intermittent therapy applied only to upper advancing portion. Exudate has ceased to reform and epithelialization has covered most of upper area. (C) Appearance after three weeks of intermittent treatment to upper area only.

VI. *Chronic Ulcerative Lesion of Leg (etiology unknown)*. (See Figs. 9A, 9B, and 9C.)

Patient R. B. was a 38-year-old colored male. Ulceration of skin over right tibia began with a small blister 6 months prior to admission. The denuding process gradually extended until it involved about one-third of the area between knee and ankle. Biopsies revealed only chronic inflammation. Antibiotic therapy was unsuccessful. The advancing edge of the lesion which extended upward, was tender to touch, and was covered with exudate.

A few cc. of concentrate rich in SK and SD were applied to the area of advancing lesion and the solution was held in place by a covering of rubber sheeting sealed with rubber cement for as many hours as possible. The treatments were repeated in this same site every 2 to 3 days for 14 days. The photographs (Figs. 9A, 9B, and 9C) demonstrate the epithelialization and regrowth of skin that occurred in 3 weeks time. No further advancement of the lesion occurred. The larger areas of the lesion were treated by skin grafting.

DISCUSSION AND SUMMARY

Against the background of previous studies of the fibrinolytic and pus-liquefying enzymatic systems elaborated by hemolytic streptococci,¹⁻⁷ the results recorded in this article demonstrate the usefulness and rapid effectiveness of the treatment of selected types of diseased states with streptokinase and streptodornase.

In patients in whom the presence of extravascular clotted or loculated hemorrhage without infection was the principal difficulty, the rapid lysis of fibrinous strands and coagulum was accomplished primarily through the action of the streptokinase system. In cases of this type the possible necessity of surgical decortication appears to have been obviated by the effectiveness of the enzymatic decortication.

When infection has been present, the mechanical effects caused by loculation were found to be complicated by the presence of a coating of tissue surfaces with the desoxyribose nucleoprotein of purulent exudates plus fibrin. And, in addition, viable organisms were present to be a constant stimulus to the formation of more exudation through which chronic infection was maintained.

The use of the streptococcal concentrates containing both streptokinase and streptodornase in eradicating the loculations or exudations of chronic infections has been referred to as *streptococcal enzymatic debridement*. Where effective application has been accomplished the following changes have been observed: a marked thinning of the exudate, an outpouring of viable leukocytes, decrease in the number of or disappearance of the locally infecting bacteria, subsequent decrease or disappearance of exudate, and rapid regrowth of tissues and epithelium.

The results strongly suggest that the effective clearing of the site of infection through enzymatic action renders the area permeable to humoral and cellular forces of both natural and specifically acquired immunity, or to circulating antibiotics, that are capable of eliminating the organisms.

The rapid rate of regeneration of the soft tissues and epithelium following

debridement has also been observed in many instances which implies that an unusual effect is exerted on fixed tissues.

Many factors and elements of this study are still in the developmental stage. Determinations of optimal dosage, frequency of administration, methods of application which bear a relation to nature, extent, and site of the disease are required before maximal effective use, as well as limitations and contraindications, can be comprehensively defined. Such additional studies are now in progress.

The authors wish to express their appreciation to the Attending Surgeons of all the Surgical Divisions of Bellevue Hospital for their constant co-operation and advice, and in particular to Dr. John H. Mulholland, Director of the Third Surgical Division.

Subsequent articles on the results obtained in these series of studies will, through co-authorship with our surgical associates, include detailed reports of factors pertinent to a comprehensive surgical analysis of each of the groups of patients that have been treated.

BIBLIOGRAPHY

- ¹ Tillett, W. S., and S. Sherry: *J. Clin. Investigation*, **28**: 173, 1949.
- ² Sherry, S., W. S. Tillett and L. R. Christensen: *Proc. Soc. Exp. Biol. & Med.*, **68**: 179, 1948.
- ³ Tillett, W. S., S. Sherry and L. R. Christensen: *Proc. Soc. Exp. Biol. & Med.*, **68**: 184, 1948.
- ⁴ Christensen, L. R.: *J. Clin. Investigation*, **28**: 163, 1949.
- ⁵ Sherry, S., A. Johnson and W. S. Tillett. (In press.)
- ⁶ Tillett, W. S., and R. L. Garner: *J. Exper. Med.*, **58**: 485, 1933.
- ⁷ Tillett, W. S., S. Sherry, L. R. Christensen, A. Johnson and G. Hazlehurst: The findings reported in this article were, in part, presented at a Meeting of the Association of American Physicians held in Atlantic City, N. J., May 3, 1949.