THE UNIVERSITY OF MINNESOTA

GRADUATE SCHOOL

Report

of

Committee on Examination

This is to certify that we the undersigned, as a committee of the Graduate School, have given George Dixon Mahon, Jr. final oral examination for the degree of Master of Science in Surgery. We recommend that the degree of Master of Science in Surgery be conferred upon the candidate.

Minneapolis, Minnesota

May 23 1911

W. E. Lister Chairman

F. C. Warner

M. L. Henderson

Conrad Jacobson

REPORT

OF

Committee on Thesis

The undersigned, acting as a Committee of the Graduate School, have read the accompanying thesis submitted by George Dixon Mahon for the degree of Master of Science in Surgery. They approve it as a thesis meeting the requirements of the Graduate School of the University of Minnesota, and recommend that it be accepted in partial fulfullment of the requirements for the degree of Master of Science in Surgery.

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7-20 2M

T H E S I S

ELEPHANTIASIS

A CLINICAL REVIEW AND AN ATTEMPT AT EXPERIMENTAL REPRODUCTION

George Dixon Mahon

Submitted to the Graduate Faculty of the University of Minnesota in partial fulfillment of the requirements for the Degree of Master of Science in Surgery.

May, 1921.

History of the Disease.

The term, elephantiasis, was not unknown to Celsus, who in a brief way described leprosy under that name. The same mistake in the use of the term was made by Archigenes, Areteus and Galen, though some passages in Galen's writings are not unlike descriptions of the disease as we know it.

Throughout the Middle Ages the authors spoke of elephantiasis, but made no effort to differentiate it from leprosy, and we can not know whether they thought the two diseases divergent forms of the same morbid process. The Arabian School described exhaustively the disease that corresponds to elephantiasis in the modern sense, under the term "da-al-fil", but did not clearly differentiate it from leprosy and other skin conditions. In fact the two diseases were not differentiated until the eighteenth century when Hillary, Hendy and Rollo wrote excellent articles on elephantiasis, and, at a little later time, Alard gave a good description of leprosy. The differentiation of the two diseases was further simplified by the writings of Danielssen, who clearly defined leprosy, and by Duchassaing, who made an excellent contribution on elephantiasis. Even this did not suffice, for no less an authority than Virchow thought fibroma molluscum should be described under the term elephantiasis, and in very recent literature some authors, in describing certain cases of elephantiasis, take the trouble to differentiate

it from leprosy.

Recently the term "elephantiasis nostras" has been added to the literature and has been applied by Unna to that form of fibromatosis which develops following erysipelas or recurring erysipelata, independent of any previous venous or lymphatic stagnation, this term being used independently of elephantiasis arabum which includes all other forms with the exception of the congenital types.

Manson added to our confusion when he ascribed certain cases of elephantiasis indirectly to filarial disease. These cases were, of course, observed in the tropics, and immediately caused wide spread attention which tended to revive the study of elephantiasis. Some enthusiasts were wont to describe elephantiasis occurring in the tropics, where filarial disease is common, as elephantiasis and to include the sporadic cases under the term pseudo elephantiasis. There was much opposition to this nomenclature from the beginning, since many authors did not place as much importance upon the filaria as a causative agent as did Manson. Later Manson was not so positive that filaria were directly responsible for the disease, but thought they were at least a predisposing factor. Since, many authors in presenting case histories apologize that their patients were never in the tropics, thus leaving the impression that filarial disease and elephantiasis are closely associated in the minds of many.

Congenital Forms.

There are several forms of the congenital variety. One type involves the entire body and is usually seen in acephalic monsters. Then, there are the telangiectodes and lymphangiectodes spoken of by Esmarch, Kuhlen-Kampff, that have a slight resemblance to elephantiasis but probably are more

closely related to tumors. The form that interests us most is a congenital enlargement of one or more extremities, in otherwise healthy infants. This enlargement continues to increase as the child grows, sometimes a little out of proportion to the general rate of growth of the rest of the body. Clinically many of the characteristics of true elephantiasis are absent, but there is no reason why a true hypertrophy can not be engrafted on this condition. The pathologic picture of this congenital type is distinctly different from that seen in true elephantiasis in that it lacks the hypertrophy of the connective tissue and round-cell infiltration that is characteristic of the latter condition. I will speak of this more in detail when I take up the pathology of the disease.

Definition of Elephantiasis.

The definitions given by various authors, where no effort is made to include the etiology, are very similar. Pusey defines elephantiasis as "hypertrophy of the skin and subcutaneous tissue, produced by local circulatory disturbance, which usually not only involves the skin and subcutaneous tissue but is limited to one member or region of the body". Lutati says, "elephantiasis is a syndrome having a multitude of etiological factors and defines it as a chronic, regional, extensive and progressive hypertrophy due to inflammatory reactions of the lymphatic and vascular connective tissue, and a simple serous transudate of mechanical origin." Matas defines elephantiasis nostras as a "progressive histo pathologic state or condition which is characterized by a chronic inflammatory fibromatosis or hypertrophy of the hypodermal and dermal connective tissue which is preceded by and associated with lymphatic and venous stasis."

Etiology

In going over the literature we find that there seems to exist a confusion of ideas concerning the cause of the edema and hypertrophy that characterize the disease. Many have thought that the hypertrophy was due to the edema. Others think the edema is merely a predisposing factor. Another group of observers contend that both the edema and hypertrophy are the result of an inflammatory reaction produced by the action of pathogenic organisms. Of the latter group certain organisms are held to be almost specific in the production of the disease.

Busey and Jarish accepted the theory that the hyperplasia occurred through the increased nutritive value brought about by the lymph stasis. Pusey thought the disease might be caused by a condition that permanently blocks the lymphatics. The earlier literature contained a predominance of this idea which is criticized by Unna, who says, "Some authors recognize in the lymph stasis and ectasis of pre existing lymph spaces a sufficient cause of the fibromatosis without explaining how a lymph stasis can produce a cell proliferation, or to prove that a central blockage of the lymph can produce a peripheral stasis." That there is no clinical evidence that cell proliferation takes place in the great number of edemas of the extremities produced by chronic valvular disease, and other conditions that alter the venous return is sufficient argument for the first theory. Piery further augments this argument by experimentally proving that the tying of a vein does not cause sclerosis.

That a blockage of the lymphatic trunks is capable of producing a peripheral edema is denied by Cohnheim after exhaustive experiments. This observation has held true in my experiments, in that I was not able to produce a peripheral edema in the dog by making a complete block dissection of the inguinal glands. Doctor Judd, in a personal interview, says he has seen

nothing more than a transient edema following dissection of the inguinal lymphatics for carcinoma of the vulva and penis.

Among the authors that contend that stasis is a predisposing factor but not entirely essential, may be mentioned Matas who holds that elephantiasis is produced by, or is the result of the invasion of a region already congested and edematous, by bacteria of the streptococcal type. In his description of a classical case he goes on to say that, "the histo pathological elements necessary to complete the picture of elephantiasis are,1- A mechanical blockage or obstruction of the veins and lymphatics, usually a thrombo phlebitis, lymphangitis or adenitis. 2- Hypertrophy of the collagenous connective tissue of the hypoderm. 3- A gradual disappearance of the elastic fibers of the skin. 4--The existence of a coagulable dropsy, or hard lymph edema. 5-- A chronic reticular lymphangitis caused by secondary and repeated invasion of microorganisms usually of the streptococcal type". Certainly the review of his case histories uphold his deductions. Sistrunk holds practically the same view as does Matas but thinks the infection may be blood borne and cites several cases to support this theory. Kaposi believed that elephantiasis was due to a stagnating lymph edema produced by repeated attacks of inflammation. Verreno thinks that in the production of elephantiasis there is an"imposition on something that has been present before, either lymphatic or venous obstruction,or both" Padget thought the disease was not to be differentiated from the consequences of chronic or repeated attacks of inflammation of the integument. Virchow believed that an irritative condition existed from the first, and in cases with venous obstruction only slight injury leads to the inflammation.

The views of Matas, Sistrunk, Pusey and others are, indeed, rational, for it is easy to suppose that tissues that are congested have a lowered resisting power and are therefore more prone to infection.

Bockhart, in this connection, theorized that in tissues in which many of the lymph spaces were obliterated from congestion, and others widely dilated from the same reason, were more likely to be permanently crippled from an invasion of the part by pathogenic organisms than normal tissues.

We have a third group of observers who contend that both the edema and hypertrophy of the subcutaneous connective tissue are the result of bacterial invasion. Of these, Unna, Sabourand and Dubriel are the most pronounced in their views. Unna argues that the inflammatory reaction produced by the action of bacteria on the blood vessels, causing thrombosis and obliteration, is sufficient cause for the edema, and believes, that the edema must come from the arrest of the outflow of blood. He further believes, that the hypertrophy of the subcutaneous connective tissue is produced by repeated attacks of streptococcal infection (erysipelas, phlegmon or lymphangitis), following which, there remains an altered condition in the circulation of the part, and an attenuation of the infection which lights up from time to time, producing in the course of months or years the condition as we see it. This opinion is held by the authors mentioned above.

Now since a large group of observers believe that the entire process is due entirely to the result of pathogenic organisms, it will be well to mention the type of organism that has been cultured from the elephantiastic patients and the conditions under which they were obtained.

Dufourgere, who spent some time in the tropics, first thought that all cases of elephantiasis were ushered in by attacks of lymphangitis. While in this locality, he saw many people with lymphangitis but found that very few of them developed elephantiasis. He was able to culture from the extremities of these patients with lymphangitis during the attack of erythema, a peculiar form of coccus which he called lymphococcus. In the locality in

which he resided filariasis was also prevalent, a fact which caused him to assume that practically all cases might be caused by filariasis. He was unable, however, to find filaria in the blood of the patients with elephantiasis, so concluded that the coccus he had found in the patients with lymphangitis killed the filaria, since all the elephantiasis patients that he observed had had attacks of lymphangitis.

Dubril, whose experience was obtained from the study of elephantiasis in the tropics, was impressed with the uniformity with which the disease developed following attacks of erysipelas. From the cases of elephantiasis that were going through these repeated attacks of erysipelas or lymphangitis, he was able to culture a streptococcus from the blisters that formed as a part of the local reaction, and also a staphylococcus from the blood stream. During the intermission or quiescent stage he could not obtain any bacterial growth either from the blood or the affected part.

Bureau was able to grow a peculiar bacillus resembling the diphtheritic bacillus, which he called the pseudo-diphtheritic bacillus and to which he ascribed the ability to produce the disease. Sabourand, one of the pioneers in the study of the bacteriology of the disease, was able to grow in pure culture the "Coccus of Fehleisen" from the cutaneous tissue during the attack of recurring attacks of erysipelas. He also was unable to isolate any organism during the quiescent period. However, he believed that there were attenuated bacteria in the tissues, that would flare up at intervals. Probably he was biased in his opinions by the research work of Achalme who proved that streptococcus could lie latent in the tissues. His experimental work has been criticized by Guillet as being unscientific. Renon isolated an encapsulated diplococcus, also during the active period, which he thought might be responsible for the condition. Sanford grew pure cultures of streptococci from the

cutaneous tissue of one case in Sistrunk's series, during the attack of erysipelas.

It stands paramount that no one has been able to obtain cultures of bacteria except during the recurring active cutaneous reactions seen in the majority of cases of elephantiasis. But it must be remembered that there are a few cases of elephantiasis that occur without any local inflammatory manifestations. Sistrunk had several of this type in his series. Bacteriological studies were made in most of the cases. In one of these patients who had never had any local inflammatory condition, McGath was able to grow, in pure culture, a green producing streptococcus. In another case that had had local manifestations he was able to isolate practically the same organism, from the deep tissues during a period of quiesence.

Filariasis as a Factor in the Production of Elephantiasis.

To Manson we are indebted for his work in ascertaining the method of propogation of the filaria and also for establishing the relationship of filarial disease and elephantiasis. He found that certain mosquitoes feeding on the blood of individuals who were harboring the filarial parasite took into their stomachs countless numbers of filaria. After a time the filaria escaped from their sheath and entered the thoracic muscles of the mosquito, where they underwent a complete metamorphosis, eventuating in the formation of a mouth, alimentary canal and a tail. In about a week from the time the mosquito feeds upon the human blood, she lays her eggs upon the water, and her life cycle being complete, dies. The parasites emerge from the body of the mosquito into the water where they again gain entrance into the human body through drinking water.

Entering the human stomach they burrow through the wall and integument and enter the lymphatic trunks. In the lymphatic trunks maturity is reached, fecundation established, and in due course, young filaria pour into the lumph stream.

Manson recognized that many people who were affected with filaria were in good condition, but he established the relationship of filariasis to lymph scrotum and elephantiasis believing that both the latter conditions were due to a blocking of the lymph stream by the filaria. The plausability of such a phenomenon has, however, been questioned, first, because a central blockage of the lymphatics cannot produce a peripheral edema, and secondly, because it has been impossible to find filaria in the blood of patients with well developed cases of elephantiasis, who had, at some former time been known to have been hosts of the filaria. Manson did not attempt to explain the former criticism, but the second issue was well known to him. He defended this by saying that he thought the lymph blockage was accomplished by the death of the parent worm, which was caused by the lymphangitis observed in all cases of elephantiasis that he studied. He also thought trauma to the part that harbored the parasite would cause the premature parturition of the ova, the ova, being larger than the embryo filaria and not being possessed of the power of motion, would cause a blockage of the lymphatics.

If we assume that filaria could cause a blockage of the lymphatics and a subsequent edema, that is not sufficient to explain the connective tissue hypertrophy which is the most characteristic histo-pathologic element of the disease. We have abundant experimental proof as well as an enormous amount of clinical material to show that an edema will not excite cell proliferation.

In the review of the clinical description of elephantiasis by Manson, he says the disease is ushered in with a lymphangitis, dermatitis and cellulitis, accompanied by temperature, the symptomatology given for the entity that is called "Elephantoid Fever", a term used by Frayer. All cases of elephantiasis observed by this author had such an onset. With the subsidence of the acute condition the parts never quite attain normal proportions; each succeeding attack, coming as it does with some degree of regularity, further cripples the part, until finally there is the typical picture of elephantiasis.

This description is not unlike the cases observed by Unna, Sabourand, DeFourgee and others who rigidly contend that elephantiasis is produced entirely as the result of bacterial invasion.

If filaria could be a factor in the production of elephantiasis the most reasonable hypothesis is that the dead parent parasite might set up an inflammation. This possibility is suggested by Pusey and Rokitansky. Manson also speaks of an abscess formation seen in certain lymphatic areas that he ascribes to this condition and which he likens to a stitch abscess in which there remains in the tissue a piece of unabsorbed suture material which acts as a foreign body.

If, in spite of the proof against it, filaria does play a part in the production of elephantiasis, Unna tries to reason out its mode of action as follows: "If we assume that as usual the eruptive fever, as described by Manson, indicates the sudden saturation of the blood with the organism, this primary effect, the erysipelas-like affection of the leg for example, can only indicate, that in contrast to the rest of the body the filaria have here left the capillaries and penetrated the skin itself." This phenomenon can be more easily understood by taking into account the effect gravity might have, when one considers the most frequent locations of the malady(legs, scrotum,

breast.)

There is further clinical proof that filaria play only a small part, if any at all, in Tilbury Fox's observation made in certain tropical countries where filarial infection was very common and at the time elephantiasis was rarely seen. M. Firket in observing the negroes of the Congo, who are almost all affected with filaria, came to the conclusion that the filaria were not a detriment to good health. Like observations have been made by a number of authors.

Geographical Distribution of the Disease.

Elephantiasis has been seen in all parts of the world but as an epidemic it exists only in somewhat circumscribed areas, all of them in tropical or subtropical latitudes. Even in these, the distribution is not uniform but appears in concentrated foci, with their immediate neighborhood comparatively free from the disease. It is notable, however, that in these tropical countries its most frequent site is in low wet regions. Lallemand found no cases in two islands of the Cape Verde group, a fact he attributed to the dryness of the climate.

In the eastern hemisphere the disease is found most abundantly in Southern Asia and the East Indies. It is very common on the Arabian coast. In many parts of India, Ceylon, and along the southern coast of China the disease exists in a large proportion of the population. Wise observed that in parts of Bengal there were but few families in which the disease was not present. Of the East Indies, Sumatra and the Philippines are the worst sufferers.

In the Western Hemisphere it is widely endemic in Venezuela, Peru and parts of Brazil. Certain Islands of the West Indies are hot beds of

the disease. In the United States and Canada the disease appears infrequently and never epidemically. The patients coming to the Mayo Clinic represent most of the States without showing a predominance of any one locality.

Age and Sex.

The opinion is universal that the disease does not occur at an early age. In the cases studied in the Mayo Clinic the youngest was twelve, the oldest fifty-five. It has likewise been observed, especially in tropical countries, that men are more often affected, supposedly on account of injuries and infection to which they are more often subjected. In the cases seen here women and men were affected about equally.

Elephantiasis a Transmittable Disease.

Dubriel thought cases of elephantiasis should be isolated during the attack of lymphangitis. On one occasion he operated upon three patients within a few days and all three patients were in the same ward. One patient was operated upon for hydrocele, another for hernia, and the third for elephantiasis of the scrotum. During convalesence the post-operative hernia patient developed lymphangitis and subsequently a well marked case of elephantiasis. He made it a rule thereafter to isolate patients suffering with elephantiasis during the attacks of erythema and lymphangitis. This practice was not carried out at a subsequent time in the same hospital and the author understood that his successors had a similar experience. Hillary contends that elephantiasis was transmitted to Barbadoes by negroes from the Guinea Coast.

Tuberculosis and Elephantiasis.

Scattered throughout the literature there are case reports

in which elephantiasis developed in the presence of skin tuberculosis and tubercular adenitis. In Sistrunk's series there were two patients who had tubercular adenitis or joint tuberculosis prior to the development of elephantiasis.

Syphilis a Factor.

H.G. Adamson reported a case of elephantiasis involving both legs associated with the eruption of syphilis. This patient had been subject to recurring attacks of erysipelas as well. Arthur Francis reported seven similar cases. There was one syphilitic in Sistrunk's series.

Interference with the Inguinal Lymphatics a Factor in the Production of Genital Elephantiasis.

J.T. Windell believed that genital elephantiasis could arise from any condition that markedly interferred with the inguinal lymphatics. He thought, however, that it was a relatively infrequent occurrence, and added that no one had produced genital elephantiasis in the dog by dissection of the inguinal lymphatics. In this connection Le Plant suggested that the infection that would finally terminate in a well marked case of elephantiasis might have been introduced at the time of operation. G. Branardel, Gaucher and Meyer report cases of elephantiasis following dissection of the inguinal glands. I have found no record of elephantiasis following the dissection of the inguinal glands in this Clinic.

In Sistrunk's series of elephantiasis there were three cases that developed following surgical procedures in the genital region, one from removal of a bladder stone with subsequent wound infection, the other two from

circumcision. One of these had some lymph edema of the prepuce before the circumcision was done.

Heredity a Factor

In the cases observed in the Clinic there is not a suggestion that heredity was a factor. Nomme reported case histories of a brother and sister who had a mild degree of thickening of the skin and subcutaneous tissue of one leg. The sister had four children, all of whom had some deformity of one leg resembling elephantiasis. The fourth child was an acephalic monster.

In summarizing, we are impressed with the preponderance of data that favors the position that the edema and hypertrophy which characterize elephantiasis come as the result of the action of pathogenic organisms, even though it has not been proved that a specific organism is responsible for the disease. It is the exception and not the rule to read case histories that did not begin following lymphangitis, cellulitis, dermatitis or some manifestation of a local infection. We must remember, however, that there are a few cases that have an insiduous onset, without any symptom either local or general that would lead one to think of an infectious process. This has been observed many times. Gatanni, Clotby, and Glossi described certain cases in Egypt with such a history. Webb mentions the same type of case observed by him in India.

There is still another type of case that develops without apparent cause, but at some time during the course of the disease, the patient suffers from repeated attacks of erysipelas. It must have been this type of case that caused J.M. Bentley to say that elephantiasis was the predisposing factor to erysipelas rather than erysipelas being productive of elephantiasis.

In Sistrunk's review of thirty-three cases, he reported fifteen as occurring without an etiological factor. After we have taken up the pathology, I wish to review briefly the case histories of these fifteen patients who had elephantiasis develop without apparent cause. The other patients in Sistrunk's series developed elephantiasis following phlebitis, cellulitis, lymphangitis, adenitis, etc., so common an occurrence as not to be worthy of review in this paper.

Pathology.

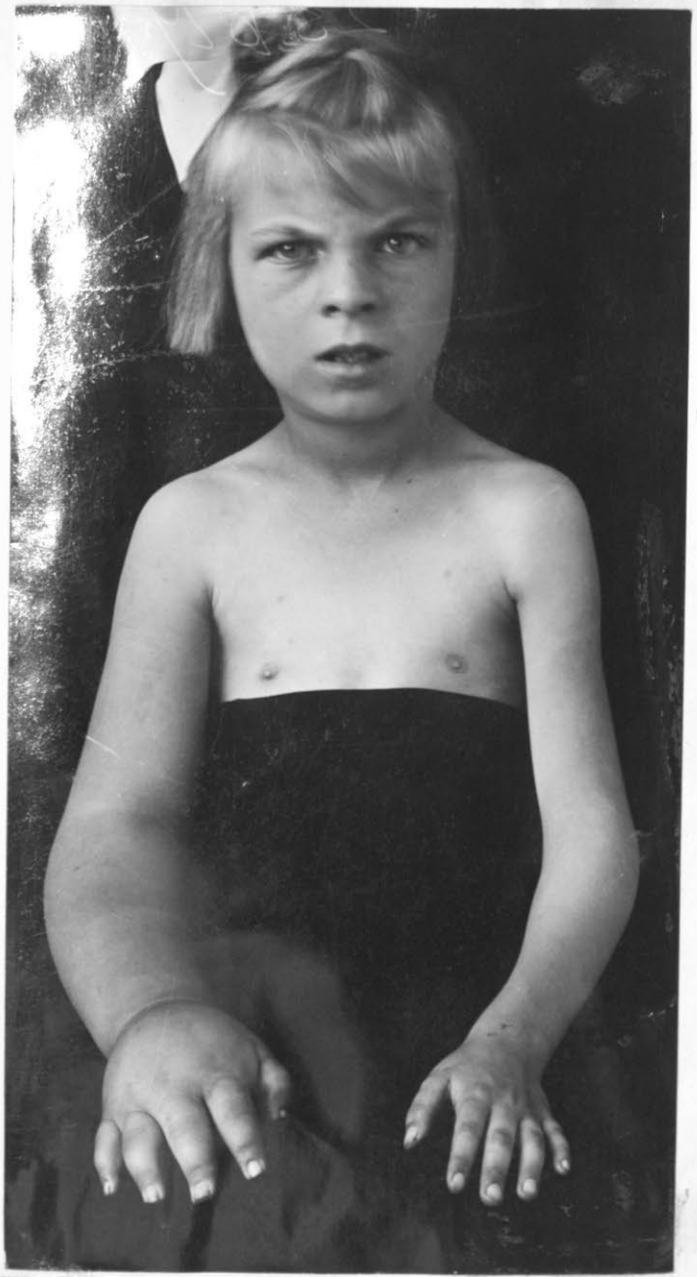
Regardless of the etiology of the disease most authors have described the same pathologic findings. Padget spoke of the elephantiastic tissue as "closely woven and very tough, and on section to exude a whitish fluid". Pusey thought that the hypertrophy of the subcutaneous tissue was the most characteristic feature, and says the hypertrophy converts the part into a dense fibrous structure in which are usually found dilated lymph spaces. The chorium is greatly thickened, and the matting together of its layers disorganize its typical arrangement. The epidermis may or may not be thickened. The sebaceous glands, sweat glands, and hair follicles may be unchanged or destroyed. Stelwagon agrees with Pusey that the chief change is the hypertrophy of the connective tissue, but also contends that the blood vessels are also changed, and adds that Mosely and Morrison found an increase in the pigment matter. Hartzell speaks especially of the changes in the blood vessels in addition to the connective tissue hypertrophy. He draws attention to a plugging of the veins with a thrombus composed of leukocytes. Elliott thought that there were more changes in the arteries than in the veins. Unna believes with Winiwarter that the condition begins quite superficially by a blocking of the veins from the inflammatory process excited by the bacteria. There is a subsequent destruction of some of the vessels, with still more edema, and the ever present bacteria

lying latent in the tissue ready to flare up, producing still more hypertrophy of the tissue, thereby interfering more with the circulation. This chain of events, or viscious circle, if you please, continues until finally there is an enormous tissue hypertrophy, with destruction of many superficial blood vessels draining the part and the resulting edema.

With the assistance of Doctor Broders, I have studied sections of majority of cases operated in the Clinic, and for the most part our findings have corresponded with the reports of the other authors.

In the congenital case reported by Sistrunk we found very little connective tissue hypertrophy in the subcutaneous tissue. The lymph spaces were somewhat dilated. There was a moderate degree of thrombosis of the vessels. The aponeurosis was thickened. There was a dearth of lymphocytic infiltration. (Figs. I & II). It is our belief, however, that the congenital type is predisposed to infection that may subsequently change it into a true elephantiasis. This is seen to take place in Case 335641, the history of which will be given.

In the true cases of elephantiasis studied, we concluded that the epidermis would most likely be thinned out where the extremity was unusually large. There was always some change in the blood vessels. Occasionally there was a marked thrombosis and lymphocytic infiltration around the vessel, and especially so in the cases that had been subject to violent cutaneous reactions. The lymphocytic infiltration was always of mild degree in the patient that had not suffered from recurring attacks of erythema, but strange to say, some of the sections representing the most marked hypertrophy were obtained from patients that had never had erysipelas, cellulitis, or any symptom that would indicate an inflammatory condition in the part. In such cases there was more evidence of lymphocytic infiltration in the deeper



Case 239819

Fig. I. Congenital type of elephantiasis.

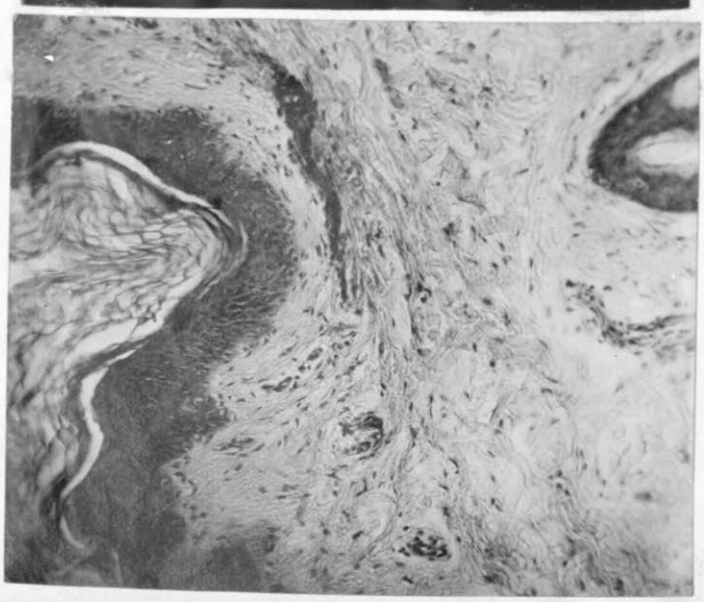


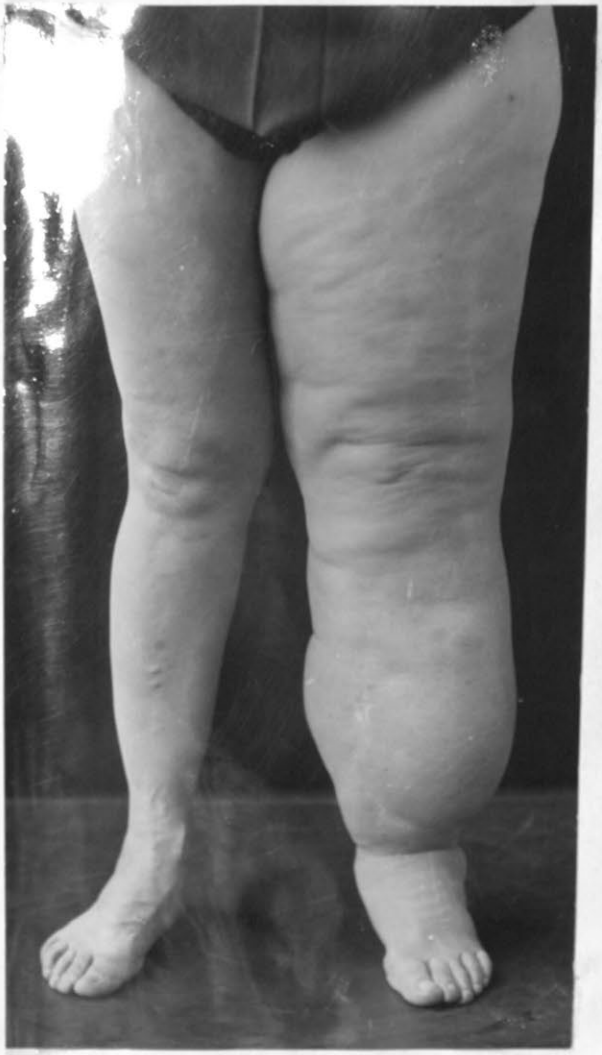
Fig. II. Photomicrograph showing trivial amount of fibromytosis but other changes seen in elephantiasis are constant. x100.

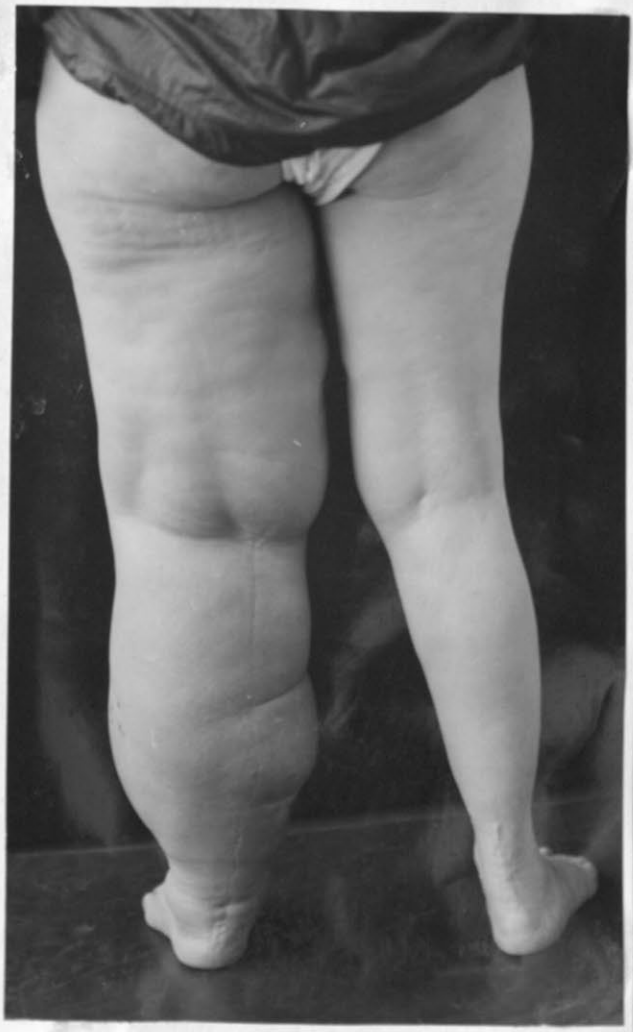
layers, and the aponeurosis was often more thickened; also there were more changes in the blood vessels of the deeper tissues than in the chorium. After consistently making such observations, and with some clinical data that supports this theory, it is not amiss to assume that in many of the patients who develop elephantiasis, the inflammatory reaction necessary to produce cell proliferation is produced by low grade organisms confined to the subcutaneous tissue and not of sufficient virulence to produce local or constitutional reactions.

Case Histories.

Case 1(310445) Mrs. C., a female aged 40 came to the Clinic complaining of marked enlargement of her left leg which had been present for twenty years. The condition began at the age of eighteen, when she awoke one morning with a sense of tightness in the right ankle and foot. In a month's time the leg had attained half its present size. There was no history of an infection of any kind. She had never suffered with tonsillitis or rheumatism. Her appendix had been removed, but with little evidence of disease. On examination here the patient was thought to be in good general condition. The leg complained of was of such enormous size as to interfere with her locomotion. There were several abrasions on the lower part of the leg, that exuded a milky fluid.

Pathology. There was a great deal of hypertrophy of the subcutaneous tissue. The blood vessels were thrombosed in places, and there was an abundance of round cell infiltration, though not so much in the chorium as in the deeper layers. (Figs. III & IV).

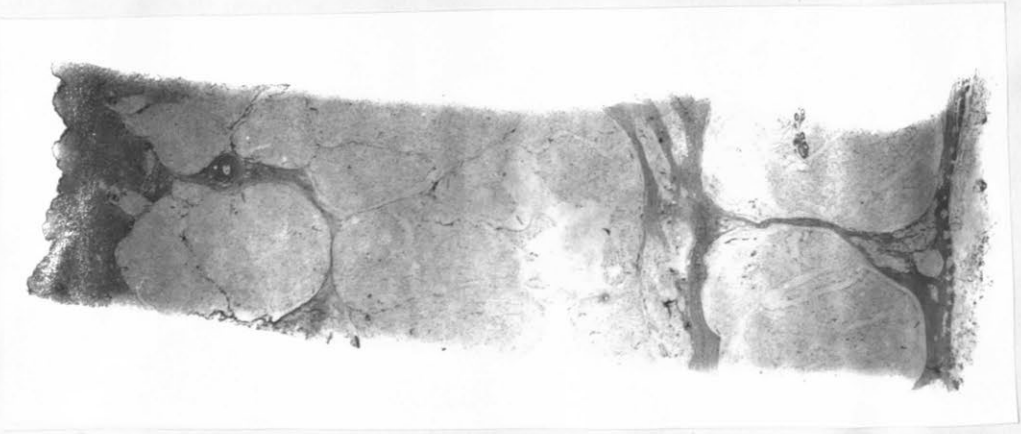




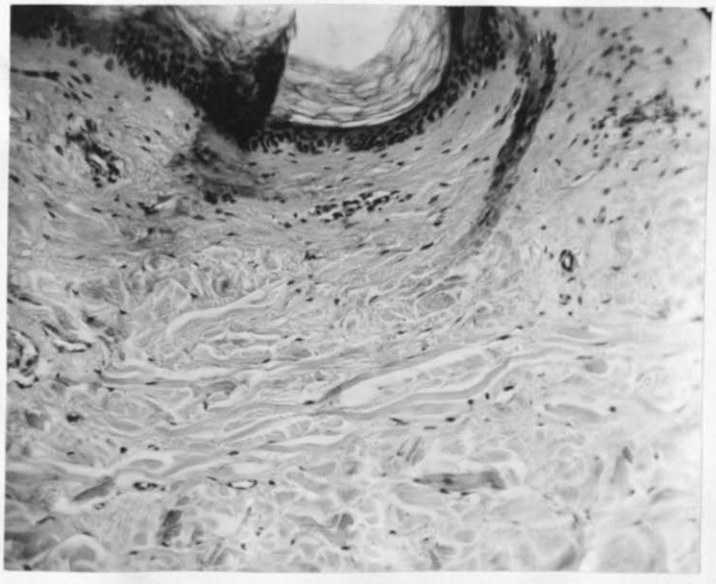
Case 310445 Figs.3

Typical case of Elephantiasis.

Figs. 4 Case 310445



a. Photomicrograph showing skin subcutaneous tissue and aponeurosis. x $3\frac{1}{2}$



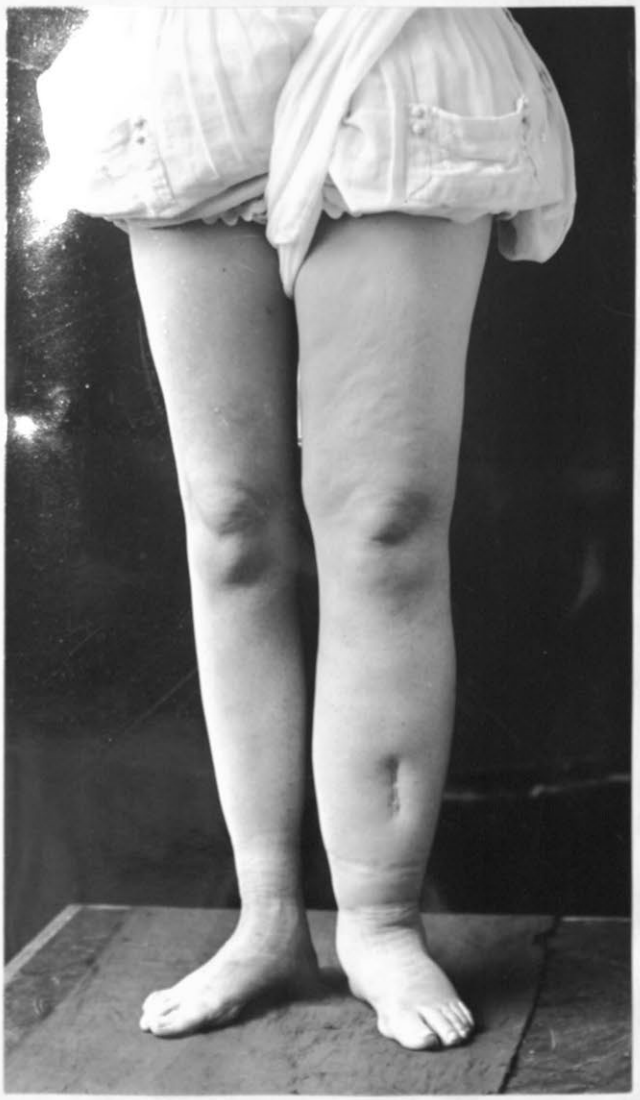
b. Photomicrograph showing preponderance of connective tissue with a mild degree of lymphocytic infiltration. The epidermis is somewhat thinned out. x100.

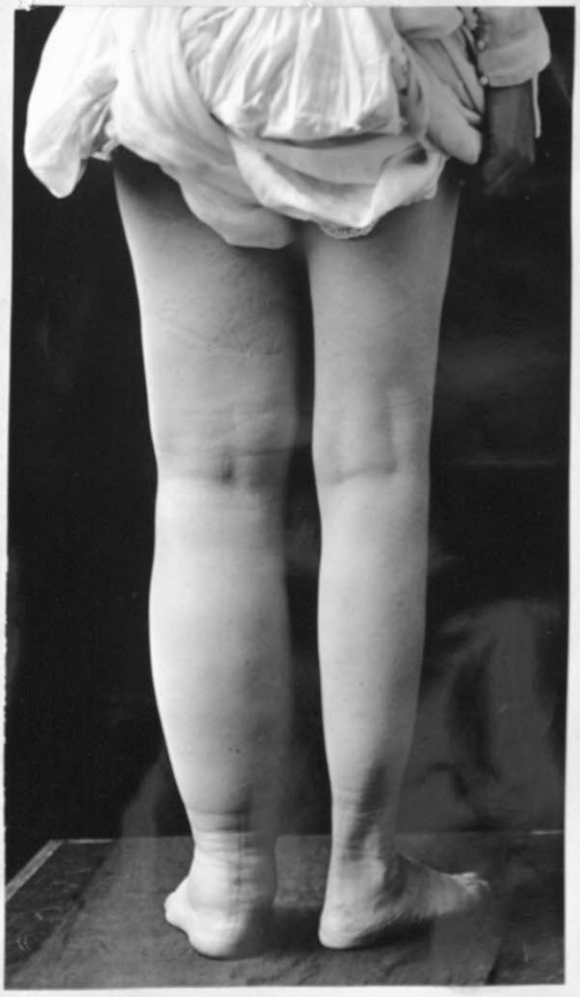
Case II.(283269) Mrs. K. This patients's history dates back sixteen years at which time she noted a gradual enlargement of her left leg. The condition has slowly progressed, and upon her visit here was of enormous size. There was nothing in her family or personal history to account for the condition. She had been married six years, with a history of a miscarriage at five months. The clinical diagnosis and the pathologic study of the tissue was almost identical to Case I.

Case III(281011) Mrs. B., age 39. Fourteen years before coming to the Clinic both legs began to swell simultaneously. The swelling was only present during the day at first. After a year from the onset, the right leg returned to normal, but the left leg has remained swollen. If the patient is off her feet for some time the swelling reduces but never quite to normal. On examination the condition was thought to be a pseudo-elephantiasis yet there was nothing in her general examination to account for the swelling. The tissue studied was not unlike the tissue from the congenital case in the series. (Figs. V & VI).

Case IV.(280999). Mr. K. Age 55. The patient was always in good health, other than a hydrocele which was operated five years ago without incident. Three years ago the patient noticed a slight swelling over the external malleolus of the left leg. In two months's time the leg had reached its present size(about twice normal size). Clinically the condition was true elephantiasis. The tissue studied showed a marked collagenous hypertrophy, with a moderate amount of round cell infiltration. Particles of tissue from the leg were placed in broth and cultured, with negative results.

Case V.(290382). Male, age 19. This boy presented himself with a history of an enlargement of both legs. The condition originated seven years ago, appearing several days after the patient had violently exerted





Case 281011 Figs. V

Pseudo elephantiasis, probably early elephantiasis.

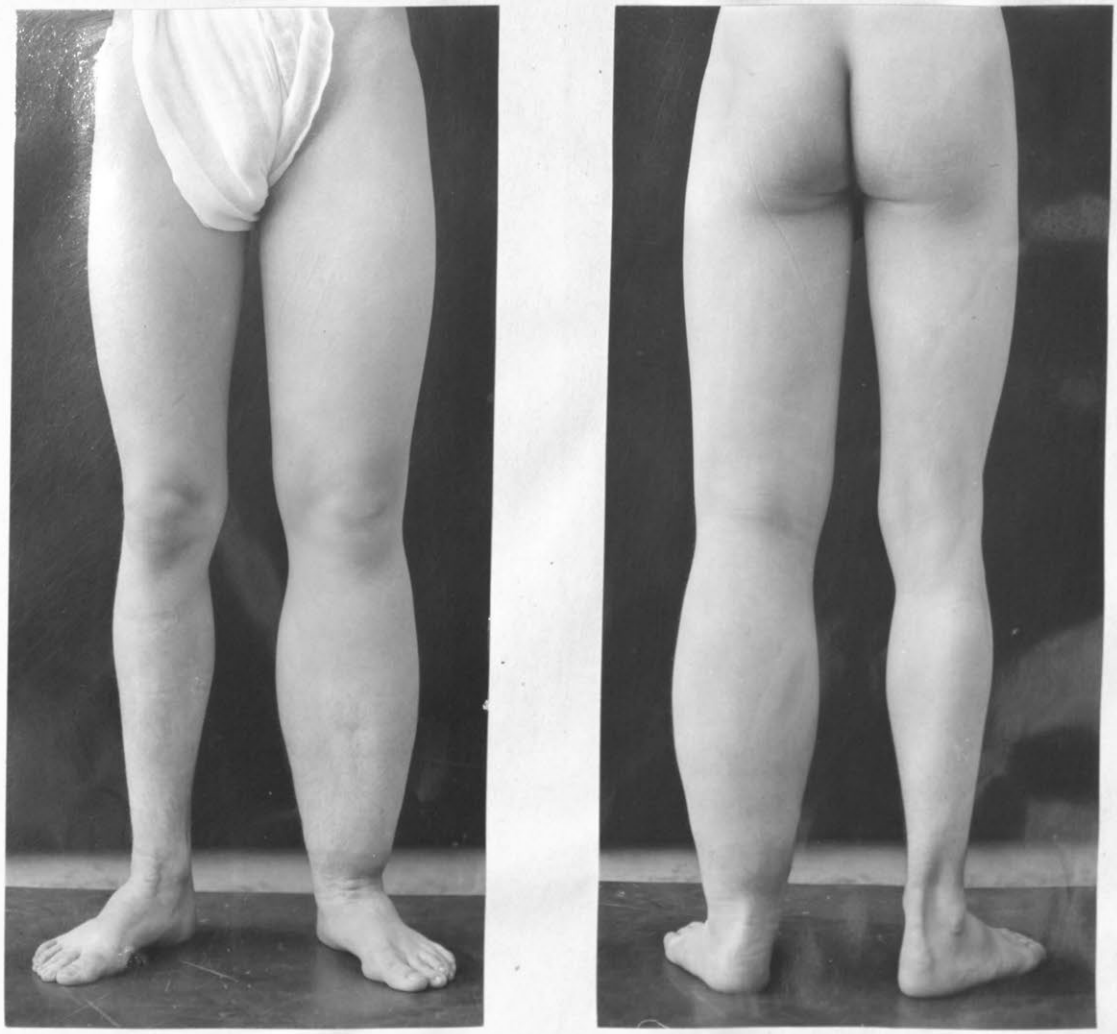
Case 281011 Fig.VI

Photomicrograph of section through skin down to and including aponeurosis. There is little connective tissue hypertrophy and the epidermis is but little affected. The aponeurosis is not markedly involved. x3½

himself. Family and personal history negative. A general examination revealed septic tonsils. Clinically the extremities were not typical of elephantiasis, but were rather soft to the touch, and was diagnosed early or pseudo-hypertrophy. The tissue examination revealed only slight hypertrophy, corroborating the clinical diagnosis.

Case VI(309183). This patient was 19 years of age and a native of Minnesota. His mother and brother were in good health. His father died of a perforating duodenal ulcer. Four years before coming to the Clinic there was a gradual enlargement of his left leg. The enlargement was progressive, uniform, and not associated with any local or general condition of an infectious nature. During the past year there had been no increase in the size of the leg. On examination the boy was thought to be in good general condition. His leg was only moderately enlarged, and it was thought staying in bed with his legs bandaged might improve his condition. This was tried for several weeks, without benefit. An operation was advised for what was thought to be an early elephantiasis. The tissue studied was typical of elephantiasis, though there was not the great amount of hypertrophy seen in some cases. Specimens taken from deep in the subcutaneous tissue just above the aponeurosis were given to Doctor Magath for bacteriological study. Within twenty-four hours he reported a growth of streptococci. It was not thought the culture came from contamination during the operation, since his wound healed primarily.(Figs. VII & VIII).

Case VII(236323). Mrs. B. age 41 years, came to the Clinic complaining of an overgrowth of her right leg. Her family history was negative. Patient had typhoid at the age of 25, with a phlebitis of the left leg as a complication. The phlebitis was troublesome for a time but finally cleared up. She also gave a history of some tonsil trouble on several occasions, though not in recent years. Six months before coming here she had pleurisy. Six

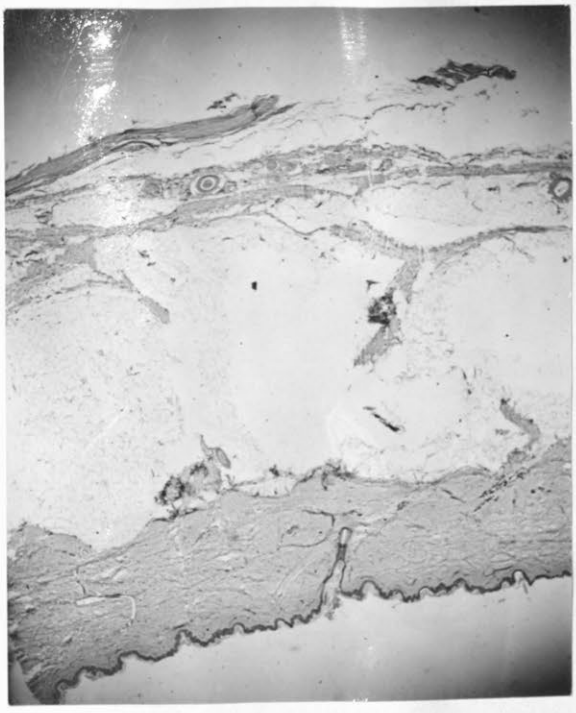


Case 309183 Fig. VII

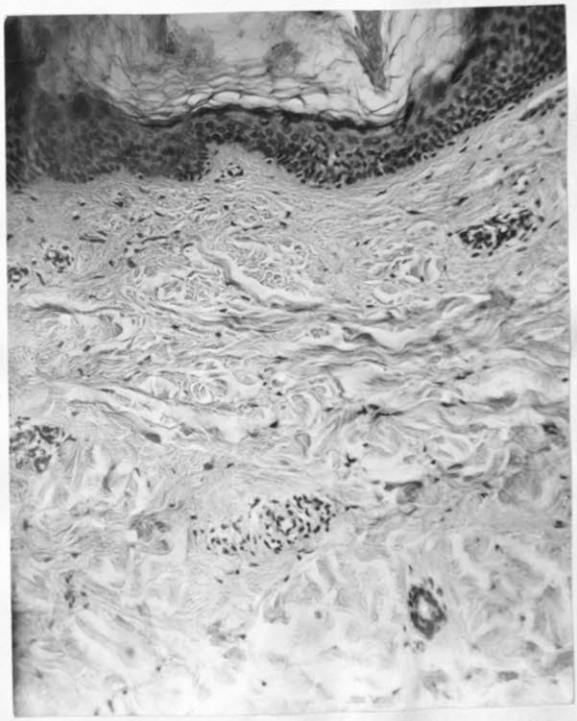
Early case of Elephantiasis

Case 309183

Figs.VIII



a. Photomicrograph showing skin subcutaneous tissue through eponeurosis. There is a moderate degree of fibromytosis together with a plugging of the vessels. x7.



b. Photomicrograph showing a definite fibromytosis together with rather marked lymphocytic infiltration. The lymphocytic infiltration is at a lower level than ordinarily. x100

years after she recovered from the typhoid, her right leg began to enlarge. This enlargement was gradual and uniform, for about four years, at which time it was half its present size. At the end of four years the patient had an attack of erysipelas in the leg. Since that time at irregular intervals these attacks have been ushered in with a chill accompanied by rather high temperature, and associated with a slight degree of lymphangitis. After each attack had subsided, the patient said her leg was somewhat larger and harder than before. The diagnosis was elephantiasis. The tissue studied was typical of the disease. Note: There are many factors in this case worthy of consideration. In the beginning of her trouble did she have a simple edema from some unknown cause, that was later converted into a true elephantiasis by repeated attacks of erysipelas? Did the phlebitis play a part? Was the entire process produced by an infection from her diseased tonsils? I believe that it would not be unreasonable to attribute the condition to any one or all three of the factors.

Case VIII(213799). This patient was a young lady, seventeen years of age and a native of Montana. Her personal and family history was negative. Her right leg had increased slowly in size for six years. There was some decrease in the size of the extremity on going to bed. In her general examination there was no evidence of any infectious process to be found. The leg was typically elephantiasis. The tissue studied was the same.

Case IX(269007). Ida S. Female, age 23. This patient was a native of Austria. She presented herself complaining of elephantiasis of the left leg, which had been diagnosed elsewhere. She had also been operated upon before coming to the Clinic, with some improvement, which was only transient. She complained of having had the trouble for about six years. During the first four years of the disease it had not attained such large size and by bandaging the extremity and staying off her feet for a few days at a time, she was able to

get along with a fair degree of comfort. There was nothing in her history to suggest a possible explanation of the disease. Clinically it was elephantiasis. The tissue studied corroborated the clinical diagnosis.

Case X(260898). Mrs. R., 39 years of age, was born in Pennsylvania. The patient was married and the mother of two healthy children. She was in good health with the exception of the trouble in her leg, for which she came to the Clinic. Twenty-one years before her visit here, her left leg began to swell. The swelling started on the outer side of the thigh. In a short time the entire leg was involved. She had controlled the size of the extremity to some degree by the use of bandages, but she was never able to reduce the limb to normal, even by prolonged rest in bed. The year before coming here she had an attack of erysipelas in the member. From the history the attack was not a severe one, and there was not noted any further change in the leg. Clinically and pathologically the condition was elephantiasis.

Note: Probably it was such cases as this one that prompted Bentley to say that elephantiasis predisposed to erysipelas rather than erysipelas being a factor in the production of elephantiasis.

Case XI(335641). This patient was a male, 22 years of age, a native of Pennsylvania, and of Jewish descent. Two months after birth, the mother noticed a swelling of the right leg below the knee. The swelling was not marked, but was uniform, involving only this part of his body. The condition continued in about that severity until had had reached the age of seven, when the right leg decreased some in size and the left leg began to enlarge. At the age of 12, the patient remembers that his scrotum began to enlarge also. From this time on he remembers having repeated attacks of erysipelas which were ushered in with a chill, and accompanied by rather high temperature, with a marked erythema.

These attacks usually cleared up in about a week, and only involved one member at the time. With each succeeding attack the parts increased in size. It is not known whether he was subject to these attacks previous to the age of 12 or not. On examination here, the condition was very typical of elephantiasis with involvement of both legs and scrotum. The scrotum was the first affected part to be operated here. Doctor Magath was able to obtain pure cultures of streptococci from the scrotal tissue. At the time of operation the patient had not had an erysipelas attack for at least a month.

There are four more cases in this series, which are quite similar in detail to the preceding ones. It might be well to mention that in one of the cases there had existed a lymph angioma since birth, the elephantiasis appearing years later.

Treatment of Elephantiasis.

The treatment of elephantiasis has been a "bugbear" to medical men and surgeons, since the beginning of medical literature. Medically they have been given alteratives, diaphoretics, stomachics, and in more recent times, glandular extract has been vigorously employed. The results were uniformly poor. Costellani reports the use of fibrolysin with fair success, but there is little in the literature to recommend its use.

It is probable that elephantiasis of the scrotum attracted the attention of the earliest surgeons, more than elephantiasis of the extremities. In the former, the condition produces marked disability earlier, and naturally greater risks were taken to effect a cure of this affliction. The vascularity of the tissues offered a barrier against its surgical treatment, before the time of the artery forceps. Edward Thompson(1838) spoke of the hugely dilated veins that were found in elephantiasis of the scrotum. Good, Eve, Key and Clot encountered little arterial bleeding, but were impressed with the hemorrhage from the enormously engorged veins.

Elephantiasis of the scrotum was first operated in this country by Picton of New Orleans, in 1837, when he successfully removed an enormous tumor. Bozeman, Whitall, and others did like operations at an early time. The mortality from sepsis and hemorrhage was high.

Webb, of India,(1859) thought operation on the scrotum often cured elephantiasis of the extremities as well, where the two were associated in the same patient. The technic of the operation has been improved but little in modern times.

The first account of the surgical treatment of elephantiasis

of the extremeties in America was by Carnochan, who in 1851, ligated the femoral artery. Carnochan thought the disease came from dilated arteries, which he found in the first case, but not in the four others of his series.

Bryant empyrically used Carnochan's method, in the treatment of elephantiasis of the limb with success, modifying the procedure by ligating the external iliac. Buchanhan ligated the external iliac, and the patient was thought to be cured; however, he later reported that the condition recurred. This method of treatment was employed both in this country and abroad but fell into disrepute, in the late sixties. Huerta made an attempt to revive this procedure in 1898. At this time Leisrink and Rooter discouraged the operation by stating after some experimental work that the lymph formation was greater after ligating the artery.

About this time there were numerous accounts of amputations being done for elephantiasis, especially where the condition had become very troublesome and was confined to the leg. Eve, in 1859, amputated above the knee, for elephantiasis associated with ulcer, affecting the leg.

In 1905, Kusnezow employed the removal of multiple cylindrical pieces of tissue from the extremity. This produced a more symmetrical appearance of the part, and in some cases, the patients were greatly benefitted. This procedure was practiced by Mikulicz, Kaposi, and others. In 1906 Rogers did much the same operation on a very marked case of elephantiasis with fair result. This is probably the first plastic operation for elephantiasis performed in this country.

From this time on, in the surgical treatment of elephantiasis two principles were aimed at: 1. To establish new lymph paths. 2. To connect the edematous elephantiastic tissues with the normal musculature below the aponeurosis.

The former principle was probably first tried in the treatment of ascities, the abdomen being opened and catgut, or T tubes being inserted- one into the abdomen and the other brought out into the subcutaneous tissue above the fascia. I do not know who was the first to employ this principle. Mauclaire employed the operation six times, using a T tube; five of the six cases soon died; one, a tuberculous ascitic patient,lived. He concluded that ascitic fluid when taken up by subcutaneous tissue was toxic.

Handly, in 1908, inserted silk strands subcutaneously, in the elephantiastic tissue to act as setons carrying the strands well into healthy tissue of the chest wall (his cases being brawny arm from carcinoma of the breast involving the axillary glands.) This method seemed very promising, and was given a thorough trial by many surgeons throughout the world. The temporary results were good, but the results were not lasting and Handly, in 1910, said, "to my mind lymphangioplasty has failed to establish its position in the treatment of elephantiasis". Even at this time, Handly thought the method supplied a channel for the lymph, but the motive force was missing, and the good the channels might do was nullified by the effect of gravity, especially in the lower extremity.

In 1912, Madden, Ibraham and Fergusson further proved that the threads acted as a wick to drain the adjoining lymph spaces for a few days and after that time, the tract was formed into a mass of fibrous tissue-inferring that the lymph flow in this area might be interferred with more than before treatment, and cited one case that was made worse by the treatment. This method is still employed in spite of the proof of its fallacy, and some authors report fair results in its use.

Working on the principle of forming new lymph channels,

Walther uses a tube and drains the lymph from the subcutaneous tissues of the extremities into the abdomen. In 1919, he reported ten cases treated by this method with fair results.

The Treatment of Elephantiasis by proximating areas of the Edematous Elephantatic tissue with normal tissue.

In 1906, Lanz made an incision in the thigh down to the femur. He then trephined the femur and inserted into the trephine holes pedunculated strips of fascia. He then made multiple incisions in the fascia. The wound was closed without drainage. Later the author thought that trephining the bone was unnecessary.

Oppel modified Lanz's method by simply incising the aponeurosis and inserting wedge-shaped pedunculated pieces of subcutaneous tissue between the edges of incised aponeurosis down in between the muscular planes. Rosanow really modified Oppel's operation, in which he inserted in between the muscular planes cellulo-aponeurotic flaps.

In 1912, Kondoleon modified the operation of Lanz by removing a great portion of the aponeurosis, about half of the entire aponeurosis of the extremity being removed. This was done by Kondoleon after seeing in old cases of elephantiasis, a very thick aponeurosis, and having failed to cure his patient by removing only small pieces of aponeurosis. Especially, though, did he rationalize his operation when he reasoned and proved experimentally that the muscles were great absorbers of lymph; hence he removed wide strips of aponeurosis allowing wide areas on each side for the leg to be in contact with normal musculature. Kondoleon reported seven cases operated by this method with success. Matas and Gessner first did the operation after the method of Kondoleon in this country in 1913. They reported two cases in which the operation gave good re-

sults. Royster, Hill, and Barber have reported cases operated by this method with success.

Sistrunk, who has had a wide experience in the surgical treatment of elephantiasis, has operated approximately forty cases by a modified Kondoleon operation. Sistrunk removes, in addition to the aponeurosis, a wide piece of skin and subcutaneous tissue nearly, though not quite as wide, as the aponeurosis. In more recent cases he has removed in addition, small sections of the aponeurosis in the iliac regions where the elephantiasis was especially pronounced in the thigh and involving the hips. Sistrunk believes the removing of large pieces of diseased skin and subcutaneous tissue is of greatest importance since large areas of tissue,which are not capable of functioning due to the destroyed vascular lymph supply, are removed.

There are several other points about the operation that Sistrunk especially draws attention to. 1. If these patients are kept in bed for a week or more, depending on the size of the leg, before the operation, the parts will be reduced in size and the operation made easier. 2. If morphin is given before operation, the shock will be minimized. 3. In the extreme cases of elephantiasis, a complete operation cannot be done at one setting and similar operations on different portions of the extremity may be done at different times. 4. The operation does not cure elephantiasis, but the condition can be much relieved, and that better results will obtain if the patients wear elastic stockings indefinitely, perhaps permanently.

Experiments.

Believing that the hypertrophy and edema which characterize elephantiasis is caused directly by the action of pathogenic bacteria, we attempted to prove this theory by animal experiments, dogs being used. From a review of the literature, I found no mention of any such investigation being made. Bockhardt injected a culture of living organisms (the coccus of Fehleisen) into the tissues of a pedunculated malignant tumor, which subsequently took on changes typical of elephantiasis. In the series of animal experimentation, an attempt was made to lower the resistance of the part by interfering with the lymphatics draining the region. Later the venous return was also partially ligated, to further lower the resistance of the part. This done, we proposed to inoculate the animals, some of them subcutaneously and others intravenously, with a green producing streptococcus that Doctor Magath obtained from the subcutaneous tissues of two patients in Doctor Sistrunk's series already referred to. Doctor Magath describes the technique used and the type of organism cultured as follows:

"A small piece of tissue taken from the leg (elephantiasis) was introduced directly and immediately into a tube of glucose broth, and incubated for forty-eight hours. At the end of that time a smear made from the broth showed numerous small short chains of streptococcus. Transfers were made by streaking a plate of blood agar; the streptococcus was present in pure culture. The colonies were minute, semi-flattened and circular, growing slowly with the formation of a slight amount of green pigment, less than streptococcus viridans but more than typical pneumococcus. The broth culture was used for the first animal injection, and sub-cultures taken from this in broth were used for subsequent injections. From another case a similar organism was isolated from a piece of tissue taken from the scrotum and this was used for the last series of animal inoculations."

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There were twenty animals used. Fourteen of this number were started in April, 1920. As has been stated, to favor the development of the organism we thought that it might help to dissect out the lymphatics of the groin of the leg to be used. In others in addition to destroying the lymphatic trunks, the femoral vein was also ligated. There were controls used. The injections of the organisms were made intravenously, and subcutaneously in different groups of the animals. The intravenous injections were made upon the evidence furnished in Sistrunk's series, for a blood borne organism to be responsible for the condition. The opposite leg from the one in which the lymphatics or veins, or both, were molested, was used for the injection. We undertook this work with the full understanding that the production of a chronic lesion in an animal offered many difficulties. Doctor Mann says "Ordinarily chronic lesions do not develop from acute lesions, unless the exciting agent is still operative. Chronic lesions seem to develop from repeated small insults." It is also a well known fact that animals may not respond to certain organisms as does man. Another difficulty was that the cultures which we used must be kept under artificial conditions for a long time and would lose some of their activity.

Experiment 1, Animal D 561. The inguinal glands and gland bearing fascia was cleanly dissected, the great vessels exposed and all fat removed from around them, then a second incision connecting the ends of the primary incision was made down to the fascia. The skin edges were turned under and the edges of the wound approximated. There was never any edema in the leg of this animal. There was injected intravenously 1c.c. of the solution of the living organism every week to two weeks, from March to November. There was never any local or general reaction. The wound was slightly infected but healed readily. On November 4th, we obtained a second culture of the same organism

from another elephantiasis patient, which we used in the experiment.(Henceforth the two cultures used will be spoken of as Culture #1 and Culture #2.) This culture was used subcutaneously. The skin was scarified and inoculated not unlike an ordinary vaccination. At two weekly intervals the dog was inoculated either subcutaneously or the skin scarified and inoculated. This animal has not shown any reaction. The leg is entirely normal, aside from slight scarring from the operation and scarification.

Experiment 2, Animal D 566. The same experiment was carried out almost identically as in Experiment 1. This dog did have a slight edema of the entire leg appearing on the third day after operation and lasting for seven or eight days. Also on one occasion there was a scab in one of the scarified and inoculated areas, showing some slight reaction. Both of these dogs have remained in good general condition.

Experiment 3, Animal D 577. On the fifth of March 1920, the glands were removed cleanly from the left groin. There was a slight edema after four days, clearing up in seven to eight days. One cubic centimeter of the same organism (culture #1) was injected subcutaneously into this animal every week to two weeks. After the third injection there appeared a slight edema of the leg, extending to the toes. This did not show up until three days after the injection. There was no local evidence at the actual site of the injection. This edema persisted for about a month and slowly cleared up, although the animal was receiving the same injections at stated intervals. The same plan was carried on until November 1920, when the same change as was made in Experiment 1 was carried out. Upon the sites of the scarified areas there developed a raw looking area about 1 cm. in diameter, that healed slowly. The dog was not used after December 22, 1920, on account of poor condition from the mange.

Experiment 4, Animal D 578. This animal was operated as in Experiment 3, and received the same number and type of inoculations up to the time of his death, which occurred May 31, 1920. There was slight edema from the operation, which cleared up rapidly. The subcutaneous injections never produced any reaction. The dog was killed accidentally.

Experiment 5, Animal D 599. In this animal the lymphatics were disturbed as in Experiment 3 and 4. There was never any edema of the leg immediately following operation. Since this animal responded slightly differently from the preceding ones, the experiment will be written more in detail.

May 3, 1920. One cubic centimeter of the culture was injected subcutaneously. There was no edema of the leg and the wound about healed at this time. At the end of twenty-four hours there was no local or general reaction. By the end of the third day there was generalized edema of the leg. The animal showed no general reaction. No fever.

May 10. The edema of the leg entirely gone. Animal injected subcutaneously.

May 13. No edema present. Again injected subcutaneously.

May 17. There was a slight general edema of the entire leg. Injected as before.

May 31. Leg entirely normal. Injection as before.

June 14. Leg normal. Reinjected.

June 28. Shows nothing. Injected subcutaneously.

July 15. Leg normal. Injected subcutaneously.

July 28. Leg distinctly larger than the other one. No thickening of the skin, more of an edema. This cleared up in two weeks, and there was nothing more of interest. The animal died the latter part of October, 1920(twenty-sixth), seven days after the last injection. At autopsy there was

free fluid in the peritoneal cavity, and a low grade peritonitis which was probably the cause of death although we could not account for the peritonitis.

Experiment 6, Animal D 600. Operated upon as the previous animal. Injected subcutaneously with a small amount of the living culture at like intervals. Aside from a slight general edema of the leg following the third injection, which rapidly subsided, there was no other incident worthy of mention. This animal died September 26, 1920, six months after the beginning of the experiment. There were no findings at autopsy that explained the cause of death. We especially looked for liver and lung changes. The leg was normal throughout, aside from a certain amount of scarring from the dissection that was made.

In the following report of a group of six experiments, the glands and gland bearing fascia were removed as in Experiments 3, 4, 5 and 6, and in addition the femoral vein was ligated. The injections were made from the same culture and in approximately the same dilution, but were all intravenous, one cubic centimeter of the culture being used in each instance.

Experiment 7, Animal D 634. May 3, 1920 glands and gland bearing fascia dissected, and the femoral vein ligated one-eighth of an inch outside the abdomen.

May 5, 1920. Leg three times normal size. An edema to be expected from ligating the vein.

May 10. Leg decreased great deal. Not more than twice normal size. 1c.c. injected intravenously.

May 13. Leg only one-third larger than normal. No reaction from the injection. Animal has good use of his limb. Injected as before.

May 17. Leg one-fourth larger than normal. Identical injection.

May 24, 1920. No edema or swelling remains. lc.c. injected intravenously.

May 31. Leg normal. lc.c. injected intravenously.

June 14. Leg normal. lc.c. injected intravenously.

June 28. No swelling or edema. lc.c. intravenously.

July 15. No swelling or edema. lc.c. intravenously.

July 28. No swelling or edema. lc.c. intravenously.

August 12. No swelling or edema. lc.c. intravenously.

This continued until October 21, 1920, when Culture #2 was used subcutaneously either by scarrifying the skin or subcutaneous injection. There has never been any further reaction, local or general, and at the present writing the animal is in good condition.

Experiment 8, Animal D 664. The same operation as in Experiment 7, as well as the same culture in like proportions were used. Animal operated May 10, 1920.

May 13. Leg twice normal size in the thigh, there being little swelling in the lower leg. Injected lc.c. intravenously.

May 17. Leg one-fourth larger than normal. Swelling rapidly going down. There is an ugly infection in the wound. lc.c. injected intravenously.

May 24. No edema or swelling except around wound. lc.c. injected intravenously.

May 31. Leg approximately normal. Wound healed. lc.c. intravenously.

June 14. Slight thickening throughout the leg. lc.c. intravenously.

June 28. Leg is swollen down to distal joint. lc.c intra-

venously.

July 15. Indurated about wound. No general swelling. lc.c. intravenously.

July 28. Slight thickening of skin not noted before. No edema. lc.c. intravenously.

August 12. Skin feels rather thick; leg slightly larger than other one. lc.c. intravenously.

September 1. Still remains slightly thickened. lc.c. intravenously.

September 15. Still remains slightly thickened. lc.c. intravenously.

October 1. Some thickening persists. lc.c. intravenously.

October 21. Leg scarified and inoculated with Culture #2. Some thickening remains.

November 4. No reaction from the last inoculation. Hardly any evidence of the scars of scarification. Same procedure carried out.

November 20. Leg the same. Injected subcutaneously Culture #2.

December 1. Leg practically normal.Injected subcutaneously, using Culture #2.

December 12. Leg practically normal. Injected subcutaneously, using Culture #2.

December 22. Leg practically normal. Injected subcutaneously, using Culture #2.

Animal died December 29, 1920. Cause of death not determined upon autopsy. Tissues of leg grossly normal.

Experiment 9, Animal D 673. Operated May 15, 1920, removing glands and gland bearing fascia left groin. Ligated the femoral vein close to the abdomen.

May 24. Three days after the operation the entire leg was twice normal size. The swelling has diminished until there is none, excepting about the wound. 1 c.c. injected intravenously.

May 30. Leg normal with the exception of a slight edema on the inner side. 1 c.c. injected.

June 14. No visible signs of swelling. 1c.c. intravenously.

June 28. Distinct edema on inner side of leg. More of an edema than a swelling since it is somewhat localized. 1c.c. intravenously.

July 14. Leg about normal. 1 c.c. intravenously.

July 28. Skin in thigh seems tight and hard. The thickening seems to be more in the skin than an edema. 1 c.c. intravenously.

August 12. Skin remains thickened from abdomen to first joint. Not much change from last injection. 1 c.c. intravenously.

September 1. Leg about normal. 1 c.c. intravenously. Changed great deal since last inoculation.

September 15. Leg about normal size. 1 c.c. intravenously.

October 1. About the same. 1 c.c. intravenously.

October 21. Leg normal. Skin scarified and inoculated with Culture #2.

November 4. Scarified points scabbed over showing some evidence of inflammatory reaction. Not much thickening about the scarified areas. Scarified and inoculated again.

November 20. Leg normal; hardly any scarring remains. No local reaction from last inoculation. 1 c.c. Culture #2 injected subcutaneously.

December 1. Leg normal. No reaction from subcutaneous injection. At the present time the same condition exists. The animal has been inoculated subcutaneously at weekly and two weekly intervals.

Experiment 10, Animal D 687. Operated May 24, 1920. Thorough dissection left inguinal region. The femoral vein also ligated close to the abdomen.

May 31. The leg began to swell in 48 hours after the operation and on the third day was twice normal size. At the present time is about one-fourth normal size. Wound not entirely healed. 1 c.c. intravenously.

June 14. Some swelling still persists. Tissue feels edematous. 1 c.c. intravenously.

June 28. Leg is swollen slightly, more of an edema than swelling. The edema appears to be more in the skin. More involvement on the inner side of the leg.

July 15. Indurated about the scar. No swelling or edema. 1 c.c. intravenously.

July 28. Skin has a thickened feel from the inguinal region to the first joint. Much different than on last examination. 1 c.c. intravenously.

August 12. Leg one-fourth larger than normal. Skin still thickened. 1 c.c. intravenously.

September 1. The same condition prevails as on the last examination. 1 c.c. intravenously.

September 15. Thickening of skin still present to about the same degree. 1 c.c. intravenously.

October 1. About the same. 1 c.c. intravenously.

October 21. Leg distinctly larger, skin slightly thickened. Skin scarified and inoculated with Culture #2.

November 4. No reaction from the scarification and inoculation. Skin has lost some of its thickened feel, hardly any larger than normal. Scarified and inoculated.

November 20. No reaction from inoculation. No change in this animal to the present time. Inoculations have been continued as in the preceding experiments.

Experiment 11. Same technique carried out as in the three previous. Aside from some swelling that took place after the operation, there was nothing of any moment. This animal died in December 1920, without apparent cause. Autopsy did not reveal any trouble to account for his death.

In two other experiments there was an attempt made to inject the culture into the artery of the leg that was operated, at the time of operation. One of the animals had a secondary hemorrhage and died on the seventh day. The other animal was not in good health, and had to be sacrificed on account of the mange, at the end of a month, so nothing came of these two experiments.

In November we started another series, in which we followed the same interference with the lymphatics and blood supply, but differed in that we used Culture #2 throughout. The injections were all made subcutaneously, using the culture in the same dilution as in the former experiments.

Dog E 69. On November 3, 1920, inguinal glands and gland bearing fascia removed from the left groin, and the femoral vein ligated.

November 4, 1920. The leg is about twice normal size. Skin scarified and inoculated with Culture #2.

November 10. There is much swelling about the wound, which is badly infected; however there is very little general swelling of the leg. Site of inoculation about healed. Subcutaneous injection.

November 12. General swelling of leg almost subsided. Site of subcutaneous injection shows some localized reaction.

November 15. Marked reaction about the subcutaneous injection. The sites of the scarification are also lighting up again, being covered with tiny blisters. General swelling and edema of no greater consequence. Animal has no temperature.

November 20. Slight induration to first joint. Site of injection about the same.

November 24. Condition about the same. Injected subcutaneously and by scarification.

November 25. No reaction from inoculation of yesterday.

December 1. Enlargement of the leg about the same. Sites of inoculation show very little.

December 8. Some edema around the operative field; wound about healed. The reaction from the inoculations about cleared up. Injected at three points subcutaneously.

December 15. Slight edema of leg, especially in thigh. No perceptible local reaction from last injection. Injected subcutaneously.

December 17. No reaction from injection. There remains some slight general edema of the leg.

December 22. Trifle thickening of thigh. Subcutaneous injection.

January 10, 1921, Leg probably a trifle thick. No evidence of local reaction from last injection. Injected again subcutaneously.

January 27. Some thickening of the thigh. Injected subcutaneously.

This animal still has some slight thickening of the leg. The inoculations have been continued as previously. It would seem if the culture of organisms could have been kept up to the virulency as in the beginning, that we might have gotten more fibromatosis from repeated inoculations, or did the animal develop some immunity to the organism?

Animal 70. Operated as Animal E 69, on November 3, 1920.

November 4, 1920. Skin was scarified on the inner side of the leg below the incision and inoculated. The leg is swollen and edematous throughout.

November 10. There is much swelling of the entire leg and especially in the region of the wound, which is badly infected. There is practically no reaction from the inoculated areas. Injected subcutaneously.

November 15. There was no sign of inflammation on the second and third days after the injection but on the fourth day there appeared an area of softening (abscess formation) to the right of the injection.

November 20. Swelling of leg about gone. There is a granulating area at the point where abscess spoken of opened spontaneously. Injected subcutaneously.

November 24. No reaction from the last injection. Injected again.

November 25. No reaction from injection of yesterday.

Leg very little swollen.

November 29. No reaction from injection. Injected subcutaneously.

December 1. Slight local thickening and edema from last injection. Leg is about the same.

December 8. The leg is normal. No reaction from last injection. Injected subcutaneously.

The animal has been injected as above at weekly intervals since, without the slightest reaction. The abscess formation is the first of the kind I have observed in these experiments. That may have come from a secondary infection, or as MacCullum has pointed out that a streptococcus infection of the skin may take on abscess formation, it being a rather infrequent occurrence. Then, too, he was speaking particularly of the erysipelas coccus.

Animal E 71. This animal was used as a control and received his first scarification and inoculation November 4, 1920.

November 10. There is a mass of small blisters at the site of inoculation. Injected subcutaneously.

November 15. The scarified points entirely healed. There is some swelling, local heat at the point of injection. Injected subcutaneously.

November 20. No reaction from last injection. Former sites of inoculation and injections healed.

This animal has been carried through the same as Animals 69 E and 70 E. Aside from the condition noted, there has been no further observations of importance. In this animal it seems one can draw the same conclusions as in Animal E 69.

On November 17, 1920, two other animals(E 97 and E98) were subjected to the same procedure. The same culture was used. A control was also used.

After the operation there was the usual edema. Also after the first inoculation or injection there was some local inflammatory reaction, which cleared up and has not been in evidence any more. One of the animals shows some slight thickening of the leg, about the same as in Animal 69.

The animals 69, 70, 71, 97, 98, and 99, the last in the series, will be followed, the inoculations repeated at intervals, realizing that we are trying to produce a chronic condition and ample time must be allowed for developments.

CONCLUSIONS.

1. The characteristic feature of elephantiasis is an hypertrophy of the collagenous connective tissue with some degree of lymph and venous stasis.

2. I believe the hypertrophy of the connective tissue and the corresponding stasis are the result of repeated insults from pathogenic bacteria.

3. In one group of cases of elephantiasis, there is an outward manifestation of infection evidenced by the erythema and adenitis. This type is more common. There is a second group, in which the disease comes on insiduously, without any local manifestation of infection. From the pathologic study of these cases, I am convinced that they too have an infection basis, which is confined to the lower layers of the subcutaneous tissue, and of such low grade as not to excite any local symptoms.

4. Anything that causes a venous stasis could be considered a predisposing factor in the development of elephantiasis.

5. From the experimental work I doubt if a dentral blockage of the lymphatics can produce permanent peripheral lymph stasis.

6. I do think that the parent worm of filaria may excite inflammatory changes, and that elephantiasis is produced in these cases by pathogenic bacteria, the filaria a predisposing factor.

7. In the Kondoleon operation, we have a means of rendering useful service to the elephantiasis patients, though the operation does not positively cure elephantiasis.

8. I believe elephantiasis can be produced experimentally, though the chief difficulty in producing a chronic lesion is in keeping the organism to be used at a uniform state of virulency.

7-20 2M

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