ELEPHANTIASIS AND THE CLINICAL IMPLICATIONS OF ITS EXPERIMENTAL REPRODUCTION IN ANIMALS

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Elephantiasis is a general term covering proliferative swelling of some part, due to a local cause and not to a general circulatory disorder. Commonly, one limb or pair of limbs is affected, the legs as a rule, but the scrotum, vulvæ and breasts are occasionally involved.

There are at least four principal varieties. Each, clinically, is much like the others, though its cause may be different. The four include: (1) the tropical sort, the basic cause of which is probably filarial infection; (2) the non-tropical sort, usually called elephantiasis nostra, the basic cause of which is unknown but which includes a sporadic form and a familial variety known as Milroy's[15, 16] or Meige's[14] disease; (3) a surgical sort, resulting from destruction of the principal lymph vessels and nodes draining a limb, whether by purely operative means or by a combination of operation, cancerous metastasis and infection in various combinations. In addition (4) there are enlargements and indurations, occasionally based upon a previous severe lymphangitis and lymphadenitis or a deep-seated thrombophlebitis, sometimes marked by partial involvement of the limb or other part and frequently by the presence of ulcers or other local sources of recurrent infection—a group far less clean-cut than the preceding.

THE DEVELOPMENT OF ELEPHANTIASIS IN MAN

Manson's[11] discovery of filarial disease in tropical elephantiasis appeared to explain the prevalence of the disease in the tropics and to leave the origin of all other forms a decided mystery. The filarial organism is known to settle at many points in the superficial tissues but tends particularly to become fixed in large numbers in the lymph-nodes and nearby in their tributary vessels. Here it excites an inflammatory reaction. A heavy infestation at the root of a limb might, therefore, by shutting off the flow of lymph through the bottle-neck at that point, cause the limb to swell. This, indeed, has seemed to be the case. In filarial elephantiasis, the limb gradually enlarges and, at some stage of the swelling, there set in, in many instances, the remarkable, recurring, self-limited attacks of so-called "lymphangitis" or "erysipelas" which complete the picture of the disease.

The Recurring Attacks of "Lymphangitis."—Today, opinion is still divided as to the relation of these inflammatory attacks to elephantiasis. The

French dermatologist, Sabouraud,[20] was the pioneer in showing that typical seizures, occurring in certain non-tropical elephantiases (members of the ill-defined fourth group), are due to the presence of bacteria in the tissues and Matas[12] has maintained that, granted some primary injurious factor, such as thrombophlebitis or a severe lymphangitis and lymphadenitis, repeated secondary bacterial infection is likely to induce elephantiasis. To him, the prevalence of bacteria in the tropics accounts for the frequency of elephantiasis there and its rarity in temperate climes. His view seems to have been shared by Sistrunk[22] whose experience with the disease was unusually large. According to this view, bacteria are necessary to the development of elephantiasis, though not its primary cause. Entering from local sores and injuries, but more often than is generally realized, through the lesions of epidermophytosis, non-suppurative bacteria, supposedly streptococci, are thought to occasion the inflammatory change which gradually closes the already disordered lymphatic channels. These changes, as Stevens[23] has shown, may represent allergic phenomena, the body being sensitized to a protein fraction of the causal bacterium, much as is the case with tuberculin, so that with every bacterial invasion a violent access of œdema occurs and fibrosis increases. However this may be, bacteria are made accountable for the repeated, self-limited attacks, much alike over long periods in any one individual, which aggravate progressively the fibrosis, hypertrophy and the deformity which mark the complete disease. Many of those who believe bacterial infection to be essential to the development of elephantiasis go farther than this, asserting, for instance, that filariasis plays no significant part in lymph-stasis, that a preliminary obstruction is not essential and that repeated bouts of streptococcal infection, whether or not observed, are its primary cause.

One objection to the bacterial hypothesis is that many instances of elephantiasis develop and remain through life without any evidence of lymphangitis or erysipelas whatever. In the sporadic cases, especially, a history of any sort of inflammatory reaction is often impossible to obtain. Gager[7] presents five instances of this sort, all among females, in two of whom the disease commenced in a very typical way at puberty. And Muller,[17] among a small mixed group in which a source of infection is usually evident, describes one of advanced deformity with which no attacks had ever been associated. Moreover, as Hope and French[8] relate in their account of a British family suffering from the hereditary form of the disease, the legs of such individuals as are subject to lymphangitis usually have been enlarged for many years before the attacks set in.

A second objection is that, except in the presence of open sores and wounds, it has seldom been possible to cultivate bacteria from the tissues of those suffering from elephantiasis. Sarbouraud's[21] few patients all had chronic sores, and though Suarez[24] in Porto Rico was successful in demonstrating bacteria in clearly septic cases (like Sabouraud's), his colleague, McKinley,[13] failed to find them in parallel cases of well-developed elephan-

tiasis of a routine sort even during quite typical attacks. Indeed, only a few investigators (Rose,[19] Acton and Rao[1]) have held it possible readily to cultivate streptococci from such limbs and have asserted that vaccines are of definite benefit in diminishing the frequency and severity of the seizures.

Lastly, the attacks, whether or not they constitute an etiological factor, have seemed to many to be allergic phenomena not necessarily of bacterial origin, but due rather to the presence in the part of some peculiar protein substance such as might arise, for instance, from the decomposition of dead filaria. (O'Connor.[18])

On only one point is every one agreed, that whether or not the attacks are truly bacterial, their frequent repetition causes the disease to take on its most typical and advanced form.

MECHANICAL AND CHEMICAL FACTORS WHICH MAY CAUSE LYMPH-ŒDEMA

From the surgical standpoint, it would appear that lymph-stasis should most readily be secured by thorough and, if necessary, repeated removal of the lymph-nodes along the course of the vessels draining a limb. Certainly, even in the absence of detectable recurrent cancer and of sepsis, axillary dissections for malignant mammary tumors occasionally result in elephantiasis of the arm. But there are no reports of success in establishing elephantiasis in animals by such means. Therefore it is pertinent to consider not only mechanical but all other causes of permanent lymph-stasis.

A disorder of chemistry and the water balance in the tissues, as described by Baráth and Weiner[3] and by Kuntzen,[10] may take place. Indeed, in the many elephantiases of a quiet, insidious onset, such an hypothesis is attractive. It has been suggested that because such states are apt to set in about the time of puberty, there may be an endocrine factor. In that case, why should only one limb so often be affected? There is no positive support for this hypothesis.

A Malformation or Varicosity of the Lymphatics May Be Present.—The frequency with which the non-tropical disease becomes established at about the time when the limbs rapidly elongate offers a certain parallelism with a rather common form of varicose veins. Yet there is no actual evidence in support of this conception of varicose lymphatics, and it is rather more likely that there may occur an incomplete development of the lymphatics in such cases, a want atoned for by the regenerative efficiency of childhood but which in later years leads to gross lymph-stasis. However, again there is no actual ground for this supposition.

A blockage occurs in the trunk lymphatics at the root of a limb or within the pelvis, as a result of unnoticed disease, or of a deep thrombophlebitis. Undoubtedly this hypothesis can and does account for much œdema of the legs. I am permitted by Dr. J. C. White, of the Massachusetts General Hospital, to describe the result of a pelvic exploration in the case of a young woman who had suffered for many years from an unaccountable elephantiasis of the left leg. He found, upon dividing the peritoneum over the left pelvic

brim, a great dilated lymphatic blocked centrally by a scar, proximal to which no lymph-vessels were visible. On pricking this huge vessel, a strong gush of lymph occurred, and he allowed it to drain into the peritoneal cavity. For

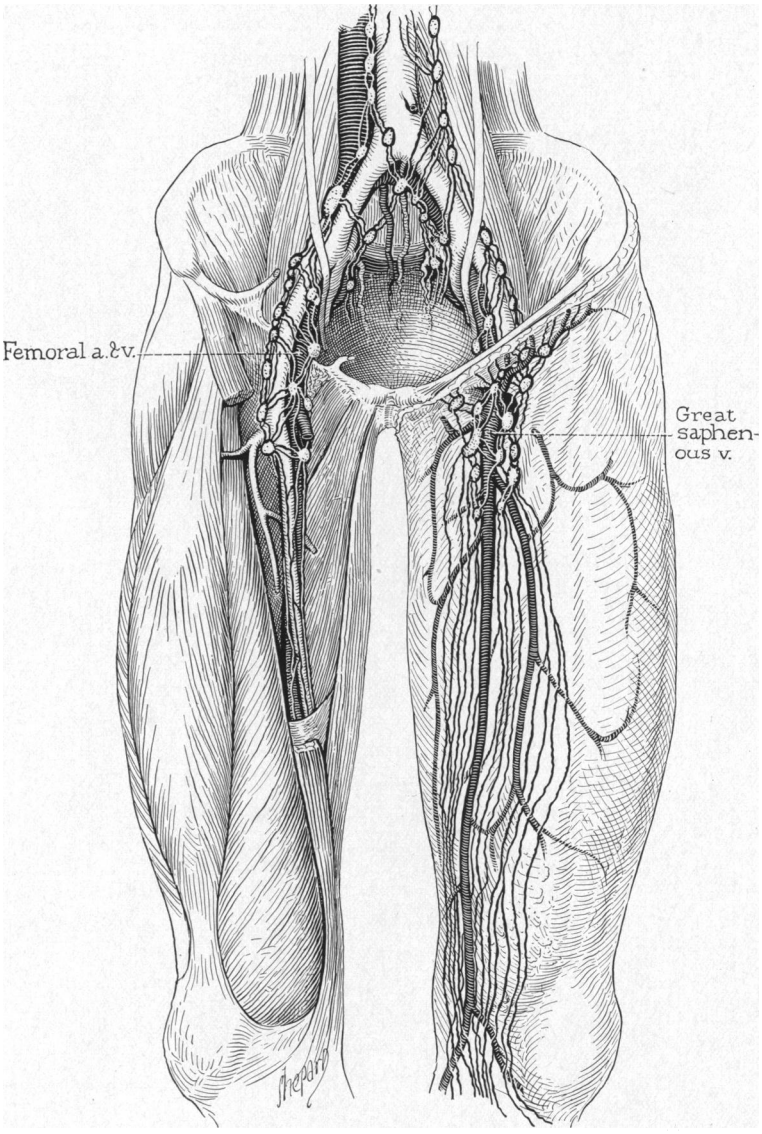

FIG. 1.—The larger valved lymphatics of the human pelvis and leg. The vessels and nodes of the pelvis are drawn after a dissection by Dr. John Warren. The superficial and deep lymphatics of the leg are after Bartels and Cruickshank, respectively. Notice at what points on the pelvic brim a local obstruction may involve the total lymphatic return from the leg. (Courtesy of the New England Journal of Medicine.)

some days, following the operation, the leg shrank remarkably but subsequently resumed its former condition. Such a state is seemingly equivalent to elephantiasis of the arm following dissections along the axillary vessels for

cancer of the breast. To cause an obstruction, the interruption need only occur at some point at which the group of primary lymph-vessels happens to be gathered into one or two channels—an occurrence unlikely but by no means impossible.

It is true also that, following phlegmasia alba dolens, the leg or legs often remain swollen. There is evidence, which one of us has presented elsewhere, that this swelling may be due to lymph-stasis resulting from damage to the trunk lymphatics within the arteriovenous sheath, but it may, in some cases at least, be due to permanently increased venous pressure resulting from partial obliteration of the principal vein and its tributaries. However, a history of phlegmasia alba dolens or anything resembling it is rarely if ever obtainable in typical Milroy's disease or sporadic elephantiasis, so that this explanation can seldom apply.

The frequency with which *some* sort of scar or fibrosis will be found obstructing the lymph-vessels of the pelvis in elephantiasis can be determined only by pelvic explorations. We are uncertain, for the moment, however, whether such a search will often be justified, for, as will presently appear, once elephantiasis is well established, the lymph-vessels of the leg itself are almost certain to have been obliterated by fibrosis. Only if investigation were made very early in the course of the disease might diversion of the lymph from obstructed peripheral lymphatics, if ever, be secured. Inasmuch as this tentative conclusion, together with an explanation of the secondary changes which give elephantiasis its peculiar character, is derived chiefly from experimentally induced lymph-stasis in the canine, a brief account of this state will here be given. It is fully described in a paper by Drinker, Field and Homans.[4]

Experimental Elephantiasis in the Dog.—Before this combined research was undertaken, Drinker and Field[5] had become expert in the cannulation of the peripheral lymphatics. They were able, with the aid of a dissecting loupe, to pick up, at any point in their course, the larger ones which accompany the blood-vessels of the dog's leg, particularly when these lymphatics were caused to take up appropriate dyes. For they had found that when a suitable dye is injected between the toes, light massage causes rapid filling of the whole lymphatic tree. Thus they were able to insert into almost any lymphatic which they could see, a fine quartz cannula and so to treat the lymph-vessels much as the physiologist experiments upon the blood-vascular system. The next problem was to find a chemical which, when introduced into the peripheral lymphatics, was capable of causing sufficient injury to both vessels and nodes to encourage their gradual obliteration by fibrosis, yet without too much toxicity for the body at large. After several trials, a 2.5 per cent. solution of quinine hydrochloride, combined with a suspension of crystalline silica-dust, was found to answer this purpose. As much as ten to twelve cubic centimetres of the solution of quinine could very slowly be introduced into the lymphatics at one sitting without causing untoward effects. Large male dogs of the German sheep type were found most

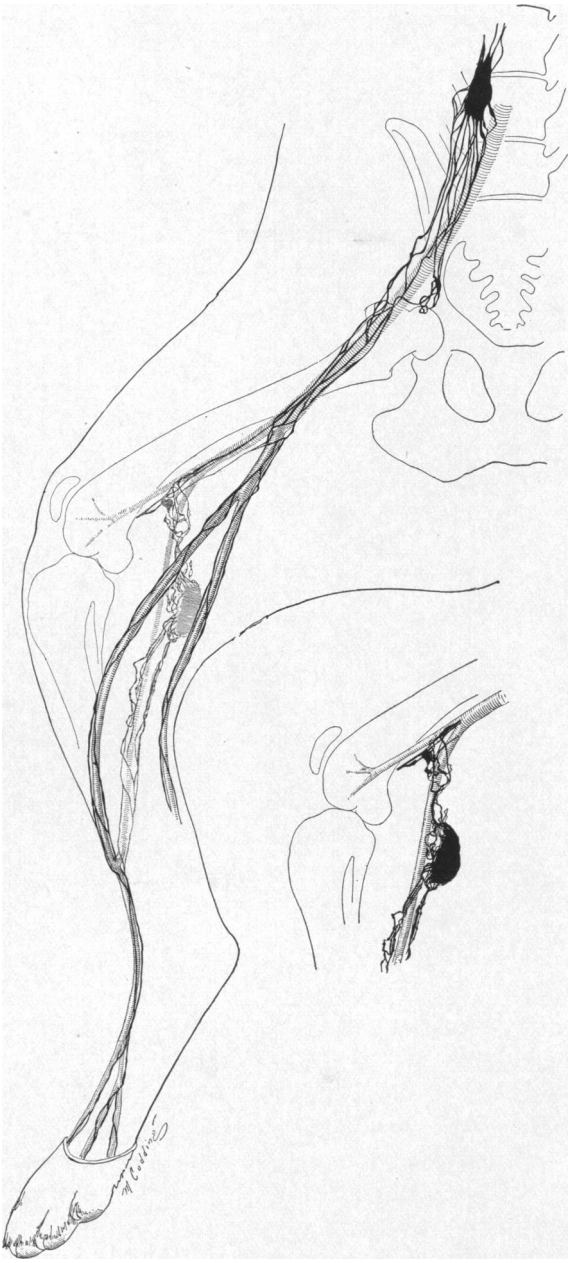

FIG. 2.—The larger valved lymphatics of the dog's pelvis and leg. After lipiodol injection of the lymphatics and operative dissections. The insert represents the great popliteal lymph-node and the lymphatics leading to and away from it. The relation of lymphatics and veins is semi-diagrammatically suggested.

suitable. All operations were performed under intraperitoneal nembutal anæsthesia.

Summary of Operative Procedures.—The first operation to be described was not used in all cases, though it may shorten the process of securing a lymphatic obstruction. In this, the abdomen is opened by a paramedian incision and the great iliac lymph-nodes, through or near which all the lymph-vessels draining the hind leg seem to pass, are excised. Even if obstruction is to be secured in one leg only, it seems better, because of anastomoses across the mid-line, to remove the nodes of both sides, tying off all the entering vessels. Such an operation causes little if any swelling, in any case only for a day or two.

The first cannulation is performed in the middle third of the thigh. Through a short incision over the femoral vessels, the femoral sheath is

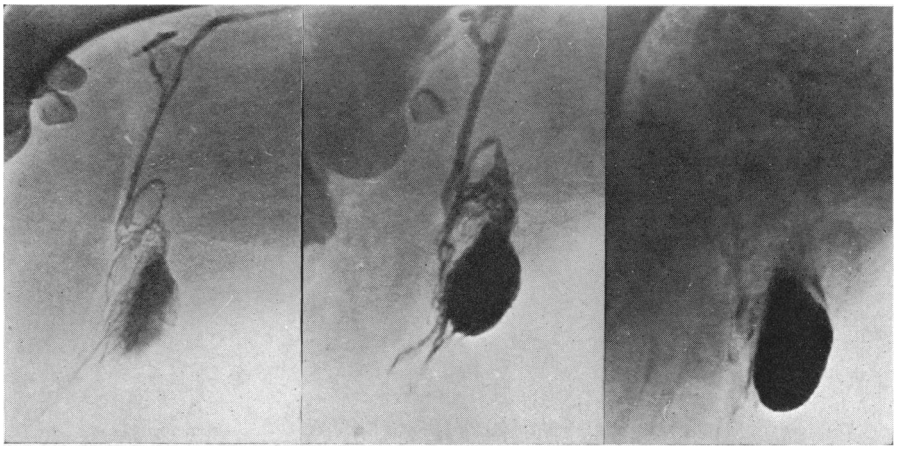

FIG. 3.—The distention and destruction of lymphatics behind an obstruction. At the left, the popliteal node and lymphatics several days after an obstruction has been established in the mid-thigh. In the centre, the same, two weeks later. At the right, the same, four weeks later. Röntgenograms, after thorotrast injections.

opened and search made for the larger lymphatics. These, three or four in number, may lie in front of, behind or between the artery and vein, communicating with each other in most cases. A decided advantage of the pelvic procedure is to render these somewhat dilated. Even then, it is seldom possible to cannulate more than two lymphatics, for what sometimes appears to be a single trunk will often, on dissection, turn out to be a plexus of fine thin-walled uncannulatable vessels. After injecting three to five centimetres of 2.5 per cent. quinine slowly into each vessel and a similar quantity of silica-dust suspension, a fair degree of swelling will follow, but will again subside, perhaps in three to four days.

Following this treatment of the main trunks, attention is now directed to the more peripheral vessels. Examination of Fig. 2 will show the many regions in which these can be approached. A superficial vein is always the guide. Naturally, the number of operations required varies from animal

to animal; but in all cases, the late sclerosing effect of the silica can be counted upon to reinforce the destructive action of the quinine. As a rule, several months go by before lymph-stasis is made permanent and a typical, painless elephantiasis is established. Thereafter, the series of clinical and pathological changes are identical with those of human elephantiasis and there have occurred spontaneously, in most cases, the identical attacks of chills, fever, local heat and swelling, which so often characterize the disease in man. These attacks and their causes will presently be described, but before this is done evidence that the experimental disease is in other respects identical with that of human beings will be presented.

As can be appreciated by comparing the lymphatics of the human leg with those of the canine (Figs. 1 and 2), man possesses many more than the lower animals. However, in one vital respect, both are alike. All lymph-vessels must come together at the root of a limb and must pass along the pelvic brim or the axilla, as the case may be, to reach the thoracic duct. That destruction of these channels where all are gathered together results in chronic lymph-stasis has repeatedly been demonstrated, in the case of the arm, by operations for mammary cancer. A case in point is that of a woman, operated upon ten years ago by one of us for cancer of the left breast. Without any evidence of recurrence, the left arm soon became swollen and has since then enlarged progressively. The subcutaneous tissues are greatly thickened and indurated, the skin hypertrophied. Recently two typical attacks of "lymphangitis," with redness, swelling and fever have occurred. The attacks were self-limited, exactly like those of elephantiasis in the leg. Since then, at one sitting, multiple excisions of hypertrophied subcutaneous tissue and muscular aponeurosis have been performed. At the operation, trypan blue was injected under the skin in the region of the hand and wrist. It was hoped that by this means obstructed lymphatics might be demonstrated and to this end the dissection was carried through the axillary scar. No vessels were found at any point. The sclerosing process had utterly destroyed them. The dye merely drifted about—as seen in the skin—by gravity.

Such a state is exactly similar to experimental elephantiasis. In that disease, valved lymph-vessels are at first present. As seen, filled with thorotrast, which they readily take up, they appear at first greatly dilated. But in time they begin to take on a vague outline and finally disappear. (Fig. 3.) We have had as yet only one opportunity, since this work was begun, thoroughly to explore the elephantiatic leg of a human being, but the findings there were similar to those present in the dog's leg and in the arm just described. Exploration of the leg, thigh and groin revealed the usual sclerosed, lymph-soaked tissues, but in spite of the use of trypan blue, neither in the periphery nor about the femoral vessels at the groin could any lymphatics be demonstrated. The dye drifted about according to the position of the leg but found no lymph-vessels to enter.

Such being the analogies between the experimental and natural disease,

it remains to examine the changes in the tissues and the nature of the febrile lymphangitis-like attacks.

THE TISSUE FLUIDS, FIBROSIS AND THE FEBRILE ATTACKS.—Fluid can best be secured from the limb in experimental elephantiasis by pricking the shaved skin deeply with a large needle. It is a little bloody at first but soon becomes clear. Followed in this way, the fluid has been found to contain steadily increasing amounts of protein. In our animals, the protein has always reached a level of 3 per cent., and, upon the establishment of febrile attacks, of 4 per cent.* As the tissue fluid has taken on more and more nearly the character of blood serum, the deep skin and subcutaneous tissues have steadily become more and more fibrosed, showing that the connective tissues are actively proliferating in so highly proteinized a medium.

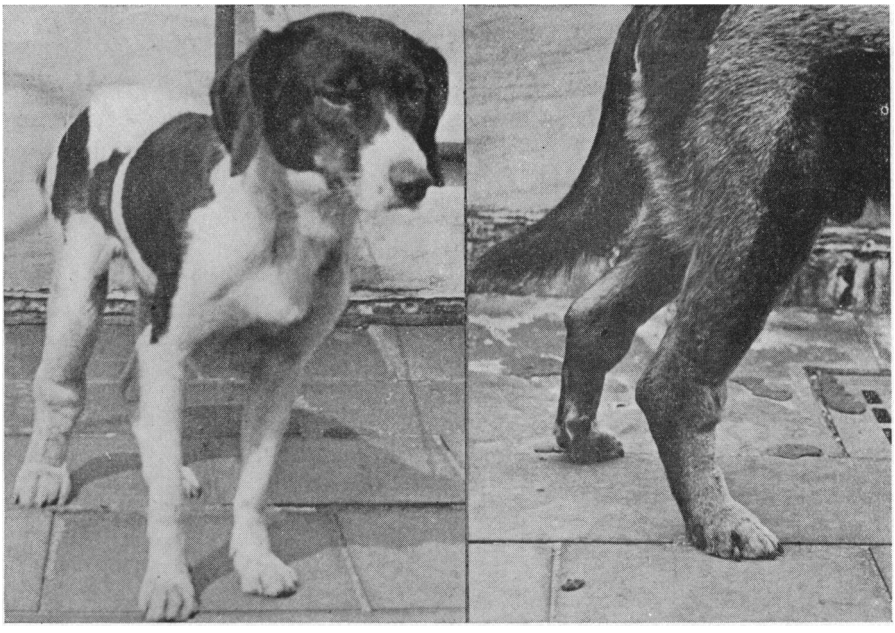

FIG. 4. FIG. 5.

FIG. 4.—Early elephantiasis. In this animal, an attack can be induced only if at all by the injection of a large dose of the appropriate bacteria. He has had no spontaneous febrile attacks.
FIG. 5.—Early elephantiasis. Soon after this photograph was taken the animal experienced a spontaneous febrile attack.

From the little we know of the fluid in human elephantiasis, it appears that here the same change occurs. We are indebted to Dr. J. C. White, of the Massachusetts General Hospital, for a report upon two patients, one of which has already been mentioned earlier in the text as presenting at the pelvic brim a dilated, obstructed lymphatic. The lymph from this vessel showed a percentage of 5.5, and there was 4 per cent. for the tissue fluid. Another of Doctor White's patients gave a protein percentage of 3.5 on one

* The detailed chemistry and cytology of this fluid is described in a paper by Drinker, Field, Heim and Leigh,[6] now in process of publication.

occasion and on another, 4. One of our own patients gave a fluid of 2.7 per cent. protein and recently an advanced elephantiasis in a young woman has come under our notice in which the fluid showed 3.4 per cent. of protein. It is of a good deal of interest to compare such findings with those of Zimmermann and De Takáts[25] in experimental venous thrombosis. They found that with increasingly severe and widespread venous obstruction went correspondingly high percentages of protein in the tissue fluids. Percentages over 3 were common and in such cases blood corpuscles were often present. To the retention of such fluids in the tissues Zimmermann and De Takáts[25] attribute the severity of the œdema and the resulting fibrosis.

The protein percentage of normal tissue fluid and lymph being around one, it is clear that when capillary permeability is greatly increased or when lymphatic obstruction occurs, the tissue fluids tend to acquire so high a percentage of protein as to resemble blood serum and a pronounced fibrosis of the tissue results. But this combined change has other effects. It leads to the establishment of attacks, the infectious nature of which has now been proved.

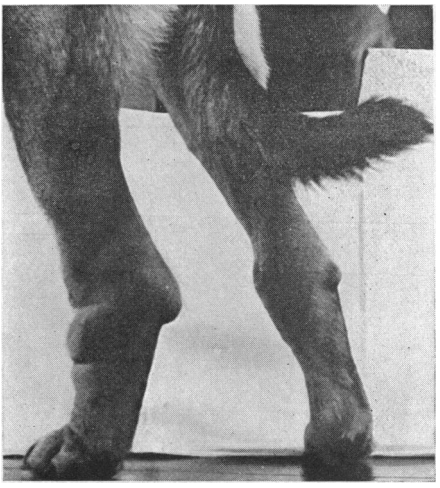

FIG. 6.—Advanced elephantiasis, in both legs, the left showing the greatest development. Febrile attacks had been going on for six months when this photograph was taken. Since then the succeeding attacks have continued and elephantiasis has considerably advanced.

The Febrile Attacks.—The first animal of our series to attain a state of elephantiasis remained in good health for some six months. (Fig. 6.) One hot day in May, 1933, he fell sick and was found to be suffering from a high fever. He had sustained no injury nor was there any sign of a local focus of infection. The left leg (the larger of the two), became hot, swollen and sensitive to handling. The dog lay prostrated, indifferent to food and drink. A moderate leucocytosis in the systemic blood and a very high leucocytosis in the tissue fluid of the leg were observed. Subsequently many attacks have occurred, rather more often, as is the case in human elephantiasis, in hot than in cold weather.

In the animal's second attack a culture of the fluid obtained showed a moderate number of hæmolytic streptococci. It then appeared that these organisms could always be secured at the beginning of an attack but never at any other time. And at any one attack, even before the fever begins to abate, they diminish in numbers. Always the same organism is present. Always the animal, in bounding health between times, is prostrated. Always the leg is everywhere hot, swollen and sensitive. The bacteria * cultivated from this dog cause no reaction when injected into the normal leg of another animal but if injected into another elephantiatic leg reproduce the typical attack. Spontaneous seizures have occurred in two other dogs but this first one has developed the most complete and man-like disease. The skin is thrown into typical baggy folds and if the animal spends many hours rampaging about, the leg becomes enormous.

* Bacteriological studies by Doctors Drinker, Field and Ward[6] are in process of preparation.

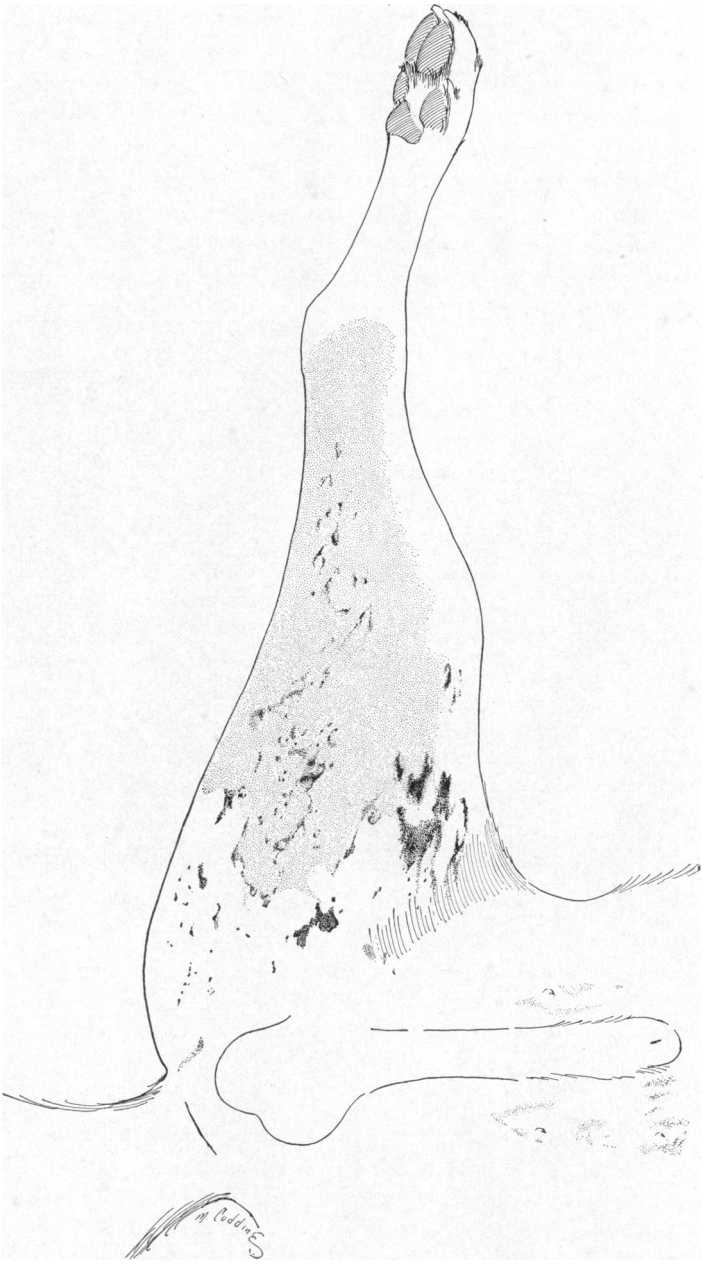

FIG. 7.—The course of a dye through the dilated lymph spaces in the skin. A sketch, two hours after the injection of trypan blue into the ankle—the leg being elevated and suspended. Streaks of the dye are seen on the abdominal wall about the external genitals.

Various circumstances modify the course of experimental elephantiasis. Dilated superficial lymph-spaces which may be covered with only the thinnest layer of skin may rupture, allowing enormous quantities of fluid to escape. In other dogs, there is a constant leak from between the toes. In such instances, attacks do not occur and the limb is less huge and baggy as would otherwise be the case. Leaks of this sort have a similar effect in human elephantiasis.

The Circulation of Tissue Fluid.—Perhaps the most practical result of these observations relates to the pathways of fluid from the leg, for these have a decided bearing upon treatment. If thorotrast is injected into the lymph-choked subcutaneous tissues and light massage is applied to the elevated leg, it can be shown that the suspension rapidly drifts into widely

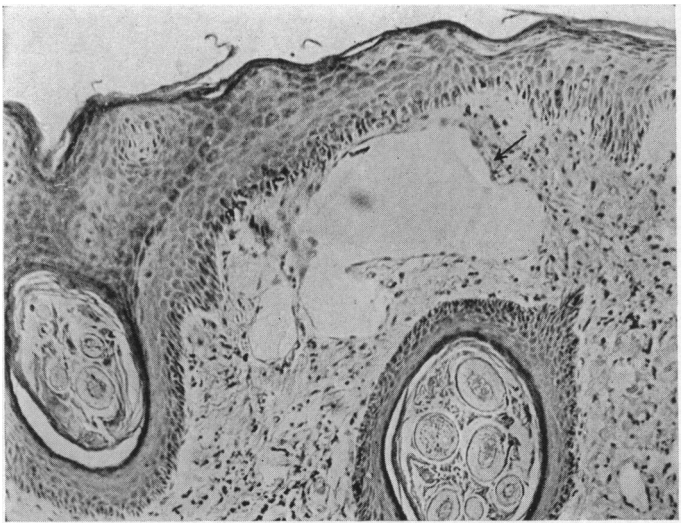

FIG. 8.—A dilated, endothelial-lined lymph space in the dog's skin. The tissue fluids circulate through such spaces by gravity. There are many more such spaces at a little deeper level.

distributed tissue spaces situated close to the surface. The thorotrast appears as a coarse mottling in the X-ray plate. But even more information can be secured by anæsthetizing the dog, injecting eight to ten cubic centimetres of trypan blue solution, suspending the leg and watching the course of the dye as it percolates through the skin. (Fig. 7.) One or two white dogs in this series have served admirably for this purpose. The dye tends to be retained in the most scarred areas and runs rapidly from looser parts. It takes, by preference, certain courses. In the instances observed, it avoids the outer face of the thigh, taking to its inner face where it shows itself in streaks, spots and blotches. It tends toward the hinder part of the thigh and in one case, rapidly colored the anus a bright blue. It colors the abdominal wall, crossing freely from one side to the other, even through the genital region. From the abdominal wall, it is diffused all over the body, finally reaching areas

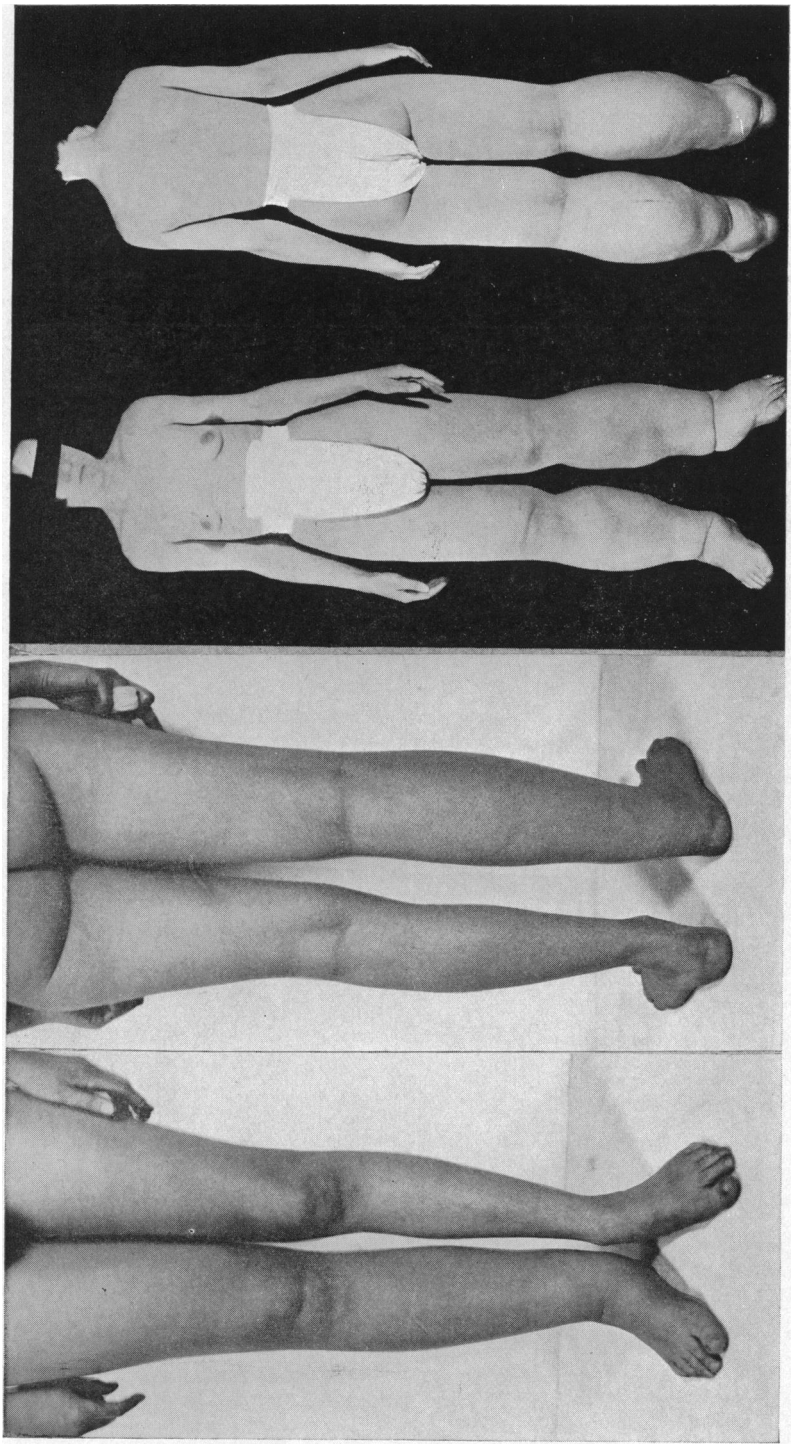

FIG. 9. FIG. 10.

FIG. 9.—C. J., elephantiasis nostra, of five years' duration in a woman of twenty-seven. A mild case. No febrile attacks. Exploration of leg after trypan blue injection revealed no lymph vessels remaining.

FIG. 10.—R. S., elephantiasis nostra, of five years' duration in a girl of nineteen. An advanced case. Two febrile attacks after the disease had developed nearly to its present stage. Pelvic exploration has shown that a lymphatic obstruction had taken place above the aortic bifurcation.

from which valved lymphatics can carry it into natural channels. But in the leg itself it follows gravity exclusively, running toward the foot quite as well as away from it if the paw is depressed.

The spaces through which the fluid mainly drifts develop, probably, from the finest peripheral endothelial-lined vessels, into a capacious, valveless series of ponds and rivers. These, as a rule, have a fibrous backing, though many are so very superficial in some part of their course as to be covered only by the most delicate layer of skin. It is these latter, doubtless, which give the appearance of deep blue spots when the blue dye is drifting through the tissues and from which leaks readily occur. It is remarkable how rapidly, through these valveless, irregular channels, the leg, *if elevated,* can be emptied. Muscular effort probably squeezes some of the fluid through such pathways toward the body but gravity is of course the governing force. (Fig. 8.)

CLINICAL IMPLICATIONS.—Judging by the course taken by colored tissue fluids in the dog and by the observations which one of us has already been able to make upon two human patients, it should be possible to discover, with the aid of dyes, the most available exits for fluid from the elephantiatic part and to plan operative treatment accordingly. Fortunately, since this paper was written and within three weeks, a patient with bilateral advanced elephantiasis has presented herself upon whom this hypothesis could promptly be tested. The accompanying photographs (Fig. 10) display the patient's disease. R.S. is nineteen years of age, married, and had a child two years ago. When the elephantiasis was already well established, before marriage, she suffered two typical attacks of fever and local inflammation of both legs. She does not think the legs were more than temporarily affected by these attacks, but pregnancy caused such swelling, including enormous enlargement of the vulvae, that delivery by Cæsarean section was required. When first seen, the surface of both legs was of almost wooden hardness, the left leg being decidedly the more tense and swollen of the two.

A 2 per cent. solution of trypan blue was injected into several places about both ankles. The left leg was slightly elevated; the right, laid flat in bed. At once the dye colored the skin of the left leg in a tide of blue which swept rapidly up to the knee. Here it flowed toward the inner side of the joint, avoiding the lateral surface of the thigh. In the right leg (not elevated) the progress of the dye was much less rapid but otherwise the same. The left leg was suspended over night at an angle of 35 to 40°; the right, left flat in bed.

On the following day, the whole left lower leg and most of the thigh were diffusely colored. Upon a pale blue background appeared darker spots, five to eight millimetres in diameter. The only regions uncolored were about the patella and upon the back of the thigh. The most heavily dyed area was just inside the knee. The patient noticed that she had to urinate often during the night and that her left flank was swollen. The calf and thigh were remarkably soft and shrunken, so that a fold of thick skin and subcutaneous tissue could now be picked up between the fingers. Thus, by gravity, much fluid has flowed out of the leg, and if the behavior of the dye is any guide, the preferred route is very superficial. Without regard to what lymphatics may be present—the failure of the posterior thigh to be colored at any time suggests that the dye has rapidly been carried away from this region by functioning lymph-vessels—it is clear, then, that the greatest possible amount of fluid-carrying skin must be preserved and the greatest possible amount of lymph-choked subcutaneous tissue and fascia must be removed.

The opportunity will soon be given to test more fully this hypothesis. The ideal operation would seem to be the turning up of long flaps of skin, as thin and as wide as

can be made without danger of sloughing. The sclerosed, lymph-soaked tissues laid bare by such flaps should now be removed, including, as far as possible, the muscular aponeurosis. Then the flaps should be replaced upon the unscarred bed. The operation is, practically, Auchincloss's[2] modification of the Kondoleon[9] procedure as practised by Sistrunk, but the object is not continuity of drainage elsewhere than in the skin itself. Nor does the plan necessarily include the introduction of fluid among the muscles, desirable as this may be. Should the fluid enter among the muscle groups, some valuable additional pumping effect might be obtained, but gravity drainage must mainly be sought. According to this scheme, if any lymphatic vessels appear to be functioning in

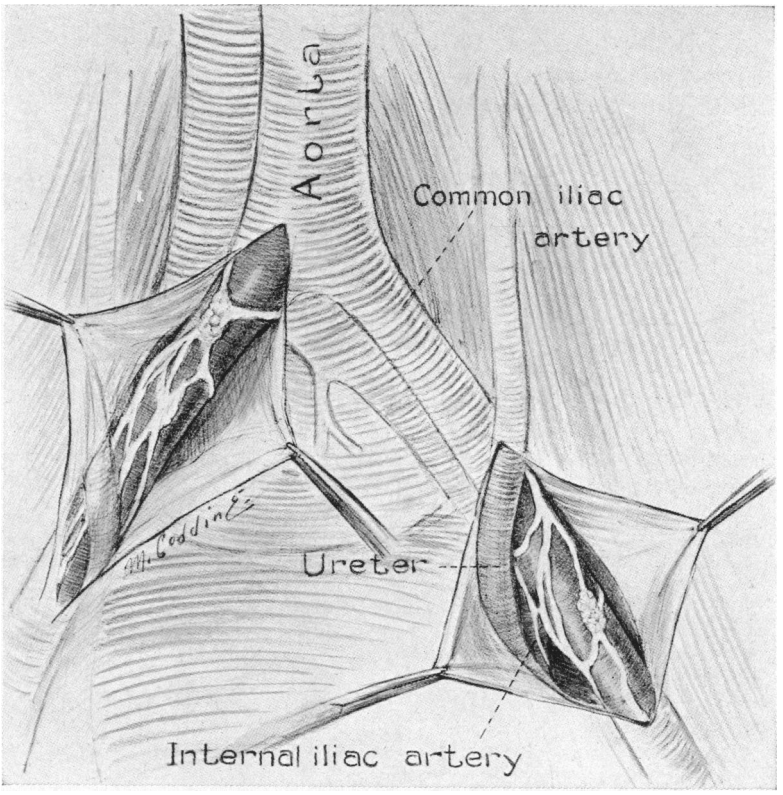

FIG. 11.—A sketch made at the operating table, in the case of R. S. (Fig. 10), showing semi-diagrammatically the greatly enlarged, sclerosed lymphatic of both pelvic brims and their relation to the external and common iliac arteries. The lymph-nodes present a mulberry-like appearance. The exact nature of the obstruction, higher up, could not be determined.

the thigh, little is to be gained by making flaps and removing tissue higher than the point from which tissue fluid and lymph are carried off with reasonable efficiency. In many cases, therefore, it may not be necessary to carry the operation much above the knee and absolute continuity of flaps from one end of the leg to the other is not vital.

In the meantime, exploration of this patient's pelvis in search of an obstruction to the lymph-stream has now been made, and with a most interesting result. The lymphatics winding about both iliac arteries were found to be enlarged to perhaps three times their normal size and very much fibrosed. (Fig. 11.) A little fluid was obtained from one by inserting a subcutaneous needle (protein, 2.9 per cent.). There was only a very small flow of lymph on the left but rather more on the right. All vessels ap-

peared valveless. The lymphatics were found greatly enlarged well above the aortic bifurcation but the risk of injuring the receptaculum chylæ prevented a further search. There must be an obstruction above to have caused so gross a change in the vessels. The lymph-nodes were fibrous, flat and considerably enlarged. Their pathology is being studied but they do not appear to be a prime factor in the obstruction.

Treatment of the obstructed lymphatics seemed to call for free opening and drainage into the retroperitoneal space. Even though the amount of lymph now carried by them is small, some permanent benefit may come from its escape. At the conclusion of the operation, the loose tissues behind the peritoneum were already saturated with fluid which was found to refill any one place as fast as it was expressed. It is to be hoped that this excess of fluid will find its way to the upper half of the body whence it should easily reach the thoracic duct.

The inference is reasonable that if exploration had been made at an early stage of the disease, before the peripheral lymphatics had been so nearly destroyed, a way could have been found to circumvent the obstruction, which must be quite local, and prevent the development of the non-reversible changes of elephantiasis in the leg. At the present stage of the disease, in this particular patient, the local operation upon the legs themselves must mainly be depended upon to modify her almost unbearable deformity.

CONCLUSIONS.—Experimental elephantiasis in the canine is identical for all practical purposes with the commonest varieties in human beings; that is, the filarial, surgical, sporadic and familial.

Experimental elephantiasis is called forth in a typical form by lymph-stasis alone, and without other influences progresses to an advanced state of fibrosis and deformity.

In the experimental and human diseases, the same high protein concentration in the tissue fluid occurs. As this concentration rises toward that of blood serum, fibrosis also increases and aggravates lymph-stasis, so that a vicious circle of protein concentration and fibrosis is set up.

Once elephantiasis is established in the experimental as well as in the human disease, there may set in the same recurrent attacks of fever and local inflammation, usually spoken of as lymphangitis. These decidedly aggravate the disease.

Hæmolytic streptococci can be cultivated from the tissue fluids in the early hours of each attack in the dog and at no other time. These same bacteria call forth a typical attack in another animal when injected, in appropriate quantity, into a lymph-obstructed leg and not when injected in even much greater quantity into normal tissue.

By analogy, it must be supposed that bacteria of a similar nature can be recovered from the tissues in human elephantiasis, provided a search is made at the appropriate stage of the attack.

The lymphatics draining the affected part, in both experimental and human elephantiasis, being disabled or destroyed, the tissue fluids circulate under the influence of gravity (aided perhaps, by muscular contractions). In the dog, once the disease is well advanced, they gravitate through wide, endothelial-lined spaces which may lie close to or actually in the skin and on reaching

normal tissues are promptly carried off. In the human being there is evidence that the same thing occurs.

It should be the prime object of treatment, after study, with the aid of dyes, of the routes most available for the tissue fluids, to preserve at operation the greatest possible amount of tissue carrying such routes and to remove the greatest possible amount of lymph-choked fibrosed subcutaneous tissue and aponeurosis incapable of carrying the fluid.

In so doing, it is probable that rather thin, long, longitudinal flaps of skin and subcutaneous tissue should be made, something after Kondoleon's plan, but the absolute continuity of such flaps from one end of the leg to the other is probably not essential.

It is unlikely that the muscles play more than an indirect rôle in favoring the circulation of tissue fluid. Nevertheless, if the fluid could actually be introduced among them, this would be an advantage.

There is evidence that lymphatic obstruction within the abdomen may often be a cause for elephantiasis nostra. Operative intra-abdominal diversion of the obstructed lymph-stream is a possibility. To be successful, it must be performed at an early stage of the disease.

Elephantiasis consequent upon repeated attacks of infection from such sources as epidermophytosis or ulcers is probably distinguishable clinically from elephantiasis primarily due to lymph stasis. In the former, the enlargement cannot develop without the infectious attacks. In the latter, the infectious attacks are often grafted upon lymph-stasis and aggravate the disease.

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DISCUSSION.—DR. EDWARD W. ARCHIBALD (Montreal, Canada).—The paper has been most illuminating, and has given us new knowledge. Of course, all of us immediately ask whether Doctor Homans can now explain to us the mode of causation of the swollen arm which occurs after breast amputations. The late Professor Halsted opined, and gave grounds for his opinion, that the trouble was due to a low-grade and widespread infection of the lymphatics, especially the deep lymphatics, resulting in extensive obstruction of these vessels throughout the tissues of the arm. Therefore, in breast amputations he advised against sewing up the wound, in order to prevent any such infection.

There are instances, which I think must be familiar to most of us, of swelling of the arm, coming on more or less acutely, five, six or eight years after a breast removal, the arm having been previously very little swollen, if at all. Sometimes, a slight coincident redness of the skin surface leads one to think there must be much truth in the Halsted theory.

The evidence put before us this morning seemed to me to indicate on the whole that we have to look for the block in the general lymphatic circulation of the extremity, rather than to one placed centrally.

I would like to ask Doctor Homans whether in his microscopical sections he could prove the existence of such thrombosed lymphatics, and, if not, has he any further fact to add which might explain the swelling of the arm.

DR. EMIL GOETSCH (Brooklyn, N. Y.).—There is one thought I would like to suggest with reference to the cause of the progressive elephantiasis experimentally produced by Doctor Homans. In the last few years I have had occasion to study thirteen cases of hygromata of the neck. These conditions are caused by factors operating in the lymphatic system and similar in some respects to the factors involved in the experimental elephantiasis. One of the explanations of the progressive local œdema and thickening of a limb is that suggested by Adami, namely, that in stagnant lymph, certain chemical changes take place with the formation of products which act as irritants on the endothelial lining of the lymphatic vessels and spaces. This thought seems reasonable for in all the cases of hygromata which I studied critically, the microscopical sections show an infiltration of large numbers of plasma cells around and in the lymphatic spaces. Secondly, there is a resultant fibrosis which further occludes lymphatic vessels and spaces, thus interfering with the normal flow of the lymph with further stagnation. Thus there is a vicious cycle produced beginning with simple stagnation of the lymph followed by irritation of the endothelial lining resulting in fibrosis and occlusion of new lymphatic paths to be followed by further stagnation with a consequent repetition of tissue irritation, infiltration and fibrosis as mentioned. In this manner, the complete and permanent blocking of the lymph channels of an entire limb may be progressively produced. These tissue changes have been observed in lymphatic tumors in the neck and it seems to me that similar factors may be in operation in certain types of elephantiasis of the limbs.

DR. EDWARD W. A. OCHSNER (New Orleans, La.).—We see a relatively large number of these cases in New Orleans. As Doctor Homans has said they are characterized by repeated attacks of infection associated with chills and fever resulting in an inflammatory reaction of the skin and subcutaneous tissue resembling the clinical entity, erysipelas. These repeated attacks of inflammation in this area of lymph stasis result in proliferation of the connective tissue of the hypoderm. This produces the thick, œdematous skin which is typical of the clinical picture of elephantiasis. The organism responsible for these repeated attacks of inflammation has been shown to be the streptococcus. Doctor Gage has isolated streptococci from several of the cases in our clinic. The organism was obtained from the deep tissues (hypoderm) of the skin. In some of the tropical countries where elephantiasis is common we find that the filaria block the lymphatics, resulting in lymph stasis, which produces a marked œdema, and according to Sir Patrick Manson this lymphœdema remains as such unless there is a secondary infection in this area with the streptococci. He has shown that it is necessary for the streptococci to infect the subcutaneous tissues before a true clinical picure of elephantiasis is present.

Acting on the suggestion of Doctor Matas, we have been able to abort the attacks of inflammation in the majority of cases in our clinic by the use of a polyvalent streptococcic serum. The method which we use in administering this serum is as follows: During the attack of chills and fever the serum is given (therapeutic dose) every twelve to twenty-four hours until the temperature returns to normal; then a therapeutic dose of this serum, usually ten cubic centimetres, is given once a month for a year. This plan of treatment has prevented recurrence of the inflammation and to a certain degree has inhibited the further development of productive fibrosis and œdema, resulting in cessation of the process.

We have not used the Kondoleon operation in any of our cases, as we believe that it gives only temporary relief. As has been shown by accurate follow-up of a large number of cases operated upon by the Kondoleon method, there was immediate improvement, but several years later the condition usually returned to the same productive lesion as before operative intervention.

DR. MONT R. REID (Cincinnati, Ohio).—In regard to the replantation of dogs' limbs. Doctor Halsted, Doctor Reichert and myself worked on this problem for two

or three years in an effort to produce elephantiasis. We found that when there was no infection the lymphatics would reëstablish themselves in from twelve to thirteen days and that, after this time, the œdema would promptly disappear. The reëstablishment of the lymphatics across the line of amputation could be easily determined by injection of the lymph vessels.

I am sure Doctor Homans is familiar with a rather remarkable case which Doctor Halsted has reported. It was a case of elephantiasis of the arm which developed four or five years after an operation for carcinoma of the breast, and was associated with the appearance of a scar in the axilla. At operation we found a recurrence which involved but did not occlude the axillary vein. I excised completely the axillary vein, with a very prompt disappearance of the œdema of the arm.

Acting on the suggestion of Doctor Matas a few years ago, we have, also, been using a vaccine to try to prevent the distressing attacks of inflammation, high fever and chills which occur rather regularly in these cases of elephantiasis.

DR. OWEN H. WANGENSTEEN (Minneapolis, Minn.).—Shortly after Doctors Brown and Horton, of The Mayo clinic, described the recognition of the presence of occult arteriovenous communications by the detection of arterial blood in the venous channels of the part concerned, I had the opportunity of observing a patient who had been operated upon some time before by the Kondoleon method for elephantiasis who presented clinical evidence of such an abnormal fistulous communication between artery and vein of her elephantisiac extremity.

The enlarged extremity was slightly redder and also warmer than the opposite normal, and on auscultation of the thigh a murmur was heard foreign to the normal extremity. Venous blood was aspirated from the superficial veins of both lower extremities and from one of the antecubital veins. The blood from the elephantisiac extremity was distinctly redder than the other two samples, suggesting the presence of arterial blood; similar samples were then drawn under oil and the oxygen-carrying capacity determined. The oxygen content of the blood from the enlarged extremity was distinctly greater, approximating that of arterial blood, as its redder color on initial withdrawal had indicated.

Exploration of the extremity along the path of the great vessels for an arteriovenous fistula was done over a considerable portion of its length without success. There had been no antecedent history of trauma. The communication undoubtedly is congenital in origin. Whether it is a single fistulous opening overlooked in the exploration or whether multiple minute communications are present remains undetermined.

In the intervening years, four other such cases have come under my observation. In one of these the opportunity was afforded of establishing with certainty the actual presence of an arteriovenous fistula in an elephantisiac extremity. The patient was a young man with von Recklinghausen's disease of multiple neurofibromas. Apart from the neurofibromas which were scattered about the body, the left lower extremity exhibited the typical posture of elephantiasis. Its enlargement had antedated the appearance of the neurofibromas in the extremity. One of the neurofibromas of the left lower thigh was frankly malignant, having undergone sarcomatous change. This extremity was slightly redder and somewhat warmer than the other; arterialized blood was aspirated from one of the superficial veins of the extremity. The malignant tumor in the leg justified its amputation. After several long and tedious dissections on the amputated extremity, a pencil-sized communication between the posterior tibial artery and its accompanying vein was uncovered.

Inasmuch as four such cases have been seen in a few years, I dare say that the occurrence of abnormal arteriovenous communications with elephantiasis is really not so infrequent. I should like to hear Doctor Homans' impression of the possible significance of an arteriovenous fistula for the genesis of elephantiasis.

DR. JOHN HOMANS.—It is quite true that there may be more than two sorts of onset in elephantiasis, one of which is infection from the beginning and the other quite obviously is lymphatic obstruction. I think the two varieties come together in the end but begin rather differently.

As far as vaccines are concerned: in the treatment of the type in which the infection is present from the beginning, I have no doubt that they may be important, but I believe the demonstration which Doctor Stevens has already given of the possibility of desensitizing these people with their own bacteria is a very interesting thing and may turn out to be more important than the use of vaccines.

As to the establishment of fibrosis in the tissue, this is actually the function of an increased percentage of protein in the tissue fluid following lymphatic obstruction. The experimental animals all have a protein percentage of between 3, 4 and 5 per cent., blood serum being only between 7 or 8 per cent. Under these circumstances, apparently the fluid acts as a culture medium for the tissues and the tissues become fibrotic. I think that is one of the reasons why the peripheral lymphatics are wiped out, even though they may have been present in the beginning. Moreover, that is why it is so difficult to tell whether the disease began as an infection all through the leg or as a central obstruction which subsequently led to the peripheral infection. But from our work on animals, we are quite sure that when it starts with a central obstruction, the resulting high percentage of protein in the tissue fluids will result finally in a complete fibrosis.