THE METHOD OF SPREAD OF GAS GANGRENE INTO LIVING MUSCLE.

[WITH COLOURED PLATE.]

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(A Report to the Medical Research Committee from a Mobile Laboratory in France.)

This contribution to the pathology of gas gangrene deals primarily with the method of spread of the acute disease into living muscle.

In our experience gas gangrene is essentially a muscle disease, and we have never seen it commence where injury of muscle could be excluded. The somewhat rare cases of "metastatic" gas gangrene, such as those described by Mullally and McNee,¹ Kenneth Taylor,² etc., come into the same category, the primary focus in every instance being in damaged muscular tissue. No example of gas gangrene beginning in, and remaining localized to, the subcutaneous tissue has been met with, and a condition spreading below the skin which is met with in base hospitals would appear to merit some special investigation before a relationship to the general type of gas gangrene can be established.

Clinically, the rapidity of spread of gas gangrene into living muscle, once the disease has begun, is so remarkable as to demand some definite explanation such as has been sought for by histological methods and is suggested here.

The varieties of the acute disease investigated in this way are sufficiently indicated in the articles published by Cuthbert Wallace, and by Frankau, Drummond, and Neligan. Part of our histological material, indeed, was obtained from the actual cases described by these writers.

The disease may commence in a wounded limb within an extraordinarily short time after the injury. The earliest case of gas gangrene examined histologically showed the condition already established three and a half hours after the wound was received, and we have seen massive gas gangrene of a limb lead to a fatal issue twelve hours after a wound of the thigh.

A point worth notice is that death may occur quickly, following a comparatively slight wound, when examination *post mortem* shows gas gangrene involving only a small bulk of actual muscle tissue. The material elaborated by the bacilli, therefore, whether it be a true toxin or not, is at any rate a powerful systemic poison. Sir Anthony Bowlby has pointed out to us that cases of this kind may very readily be mistaken for death from shock alone.

Wounds involving main blood vessels—for example, the popliteal artery—are notorious for the frequency with which gas gangrene develops in the distal segment of the limb, and it is necessary to point out here that there are differences between the spread of gas gangrene following such an injury and the invasion of living muscle. Where the main artery is cut, massive or "group" gangrene generally occurs, whole groups of muscles being involved from end to end simultaneously by the growth of organisms throughout the muscles from which the blood supply has been cut off.

The spread of gas gangrene into living and healthy muscle, with an intact blood supply, is a different and less easy problem, with the solution of which this paper is mainly concerned. With regard to this, two facts must here be briefly brought to mind. One of these is the

clinical observation, now well established and borne out by the microscope, that gas gangrene tends to spread in the longitudinal axis of muscles, so that single muscles are involved from end to end while neighbouring ones are untouched. It must also be remembered that individual muscle fibres stretch without interruption from one tendinous attachment to the other.

It is essential, in investigating the spread into muscle, to work on material which is absolutely fresh. Most of the examinations have been made on limbs amputated for gas gangrene, and brought at once to the laboratory while the healthy muscles were still contractile. Other tissues examined were either from single muscles removed by operation or from *post-mortem* examinations carried out within an hour or two at most after death. Unless fresh material is used, quite fallacious conclusions may be drawn, since, especially in summer time, the organisms proliferate and produce gas with extreme rapidity in the warm body after death.

In amputated limbs, and in the stumps left at operations, we have had ample opportunity of proving that the anaerobic organisms are present in the healthy muscle at a considerable distance from the actual seat of the gangrene. Thus the presence of the organisms in the muscles, even though abundant, does not constitute gas gangrene, and, indeed, such infected muscles may never become gangrenous.

This is well seen in amputation stumps, known to be infected, but in which no recrudescence of the gangrene occurs after the operation, in a majority of cases.

BACTERIOLOGY.

The bacteriology of the acute disease will be referred to only briefly, as so much has already been published on the varieties of anaerobic bacilli to be found. It is enough to say that all our work has been done on acute and often fulminating cases, such as are seen in casualty clearing stations on the front. In these cases mixed anaerobic infections are the rule, but sufficient work has

been done in isolating the different organisms to incriminate the *Bacillus aerogenes capsulatus* (*B. perfringens*) as the commonest and most abundant organism present. It appears often to be the only organism which is isolated from the spreading margin of the gangrene at a distance from the wound. The biology of this organism, with its powerful fermentative action on sugars and resulting evolution of gas, fits in very well with the extraordinary rapidity of spread of acute gas gangrene.

A number of experiments to reproduce a spreading gas gangrene have been carried out in animals to amplify and confirm the findings in human tissues. These will be referred to again later on.

HISTOLOGICAL CHANGES.

The material examined histologically was almost always embedded in paraffin, after fixation in 10 per cent. formalin, or in corrosive sublimate; frozen sections and tissue fixed by boiling were also used for the investigation of certain important points. Muscle taken for examination must be handled with great care or fallacies from artificial separation of the fibres may arise. The histology of single muscles, removed at operation and necessarily pulled on in the act, required, therefore, careful consideration before conclusions could be drawn from the sections. The best material was obtained from amputated limbs, in which the individual muscles could be carefully dissected, and pieces cut out with a sharp knife or razor, all pulling being avoided.

In a few cases only we have had the good fortune to

DESCRIPTION OF COLOURED PLATE.

Figures VIII, IX, and X represent the conditions found at different levels in a single block of tissue from the advancing margin of gas gangrene. Between Figure VIII and Figure IX there is an interval of 2.5 mm. of length, and the same distance between Figures IX and X.

Fig. VIII.—Normal muscle in transverse section, just beyond the edge of the spreading gangrene. (Haemalum and eosin.)

Fig. IX.—Muscle from as nearly as possible the visible advancing edge. Note the marked contrast between the dead coagulated fibres, which are separated off from their sheaths, and the paler normal fibres. (Haemalum and eosin.)

Fig. X.—All the fibres are here degenerated, but their sarcolemmal nuclei still appear intact. Separation of the fibres from their sheaths is everywhere complete. (Haemalum and eosin.)

Fig. XI.—This shows the distribution of organisms at a comparatively early stage. There are large numbers of bacilli in the reticulum, but they have not yet invaded the fibres. This stage is slightly more advanced than that depicted in Fig. X, and the nuclei of the sarcolemma have disappeared. (Leishman's stain.)

Fig. XII.—Phagocytosis of anaerobic bacilli in a zone where the process of gas gangrene has been arrested. The leucocytic reaction is in remarkable contrast with the previous figures. (Leishman's stain.)

Fig. XIII.—A late stage of gas gangrene, showing complete disintegration of muscular fibres and reticulum. In this material organisms were present in large numbers, and frequently in the substance of the fibres. (Haemalum and eosin.)

obtain a muscle with fairly long fibres, in which the advancing edge of a spreading gas gangrene could be clearly recognized. It is from these fortunate instances, however, by the examination of serial sections, that most of the information has been obtained of the method of spread. Macroscopically the appearance of this spreading margin is interesting. It is sometimes fairly sharp, but in other instances is irregular, from the process having spread further along some fibres than others. The muscle fibres at the margin are paler and duller than the normal, but the colour change is little more than might be accounted for by total absence of blood in the part involved. The outer limit of the process, while indefinite, can be mapped out fairly closely if the healthy muscle beyond is still contractile (in tissues examined very soon after amputation), as contractility is lost in the part becoming gangrenous. At the advancing edge also the muscle tissue is very much firmer to touch than the healthy fibres beyond, and this firmness passes back into the obviously gangrenous muscle behind.

When the whole of the advancing edge is cut out, along with a margin of tissue on either side of it, and examined in serial transverse sections, the appearances presented are very striking, and are shown in the first three microscopic drawings (Figs. VIII, IX, and X).

Figure VIII represents the muscle in transverse section just beyond the furthest limit of the advancing gangrene; the muscle here was still healthy and contractile. The muscle fibres appear normal, and are seen to be made up of fibrils which show as dots in the transverse section. The cracks in the fibres are artefacts produced in the cutting of the paraffin sections. They occur so constantly in transverse sections of normal fibres that they can almost be taken as characteristic of healthy muscle. The flattened nuclei of the sarcolemma are well seen, and also the interstitial tissue between the fibres, which carries the blood vessels, lymphatics, etc.

Figure IX is from a section taken from as nearly as possible the advancing edge, as seen by the naked eye. The muscle here had lost its contractility. Various normal fibres are seen, with characters as above, while others exhibit a very striking change. The staining reaction is different, being an almost uniform eosin tint, while the dots indicating the individual fibrils are lost. These fibres are not shrunken, but on measurement are often found to be somewhat swollen. In spite of this, however, these fibres are well separated off from the interstitial connective tissue, to leave what appears in the section as a clear space. Occasionally the separation of reticulum from fibre is partial, and confined to a sector only; but even in such instances the fibre still shows the uniform eosin tint indicative of degeneration. The sarcolemmal nuclei of the separated fibres still stain brightly. The contents of the spaces between the altered fibres and the interstitial meshwork will be discussed later, and it may simply be noted here that such fibres are obviously cut off from their blood supply in the interstitial tissue.

Figure X is from a section taken from the tissue $2\frac{1}{2}$ mm. behind the one just mentioned, and in it all the fibres have undergone the degenerative change described above. The fibres are all separated off completely from the interstitial tissue, which forms a regular network between them. The regularity of the network is in no way exaggerated in the drawing, and no difference would be observed in a colour photograph of many of our sections. The nuclei of the sarcolemma are at this stage stained as in the normal fibres.

In longitudinal sections of tissue taken to include the advancing edge, the process is less striking to the eye, as it is impossible to get complete lengths of fibres in any one longitudinal section. The appearances are quite easy to follow, however, having in mind the information obtained from the transverse sections. A fibre which stains normally can often be traced to a point where, quite suddenly and with a very definite edge, the colour change to the strong uniform eosin tint is met with, and the normal striation disappears. Practically coinciding with the colour change, which no doubt represents the margin of death of the fibre, the interstitial tissue is seen to separate off and leave the clear space which is so obvious and striking in the transverse sections.

The significance of these observations may now be briefly dealt with.

In transverse sections stained for organisms these are

found far beyond the edge of the gangrene in the interstitial tissue between the healthy fibres. What, then, determines the advancing death of the individual fibres? The whole question seems to us to be bound up in the contents of the spaces left between the degenerated fibres and the meshwork of interstitial tissue. The altered fibres are not shrunken, and the muscle at the spreading margin is tumid and increased in bulk. This swelling is evidently due to the extra room taken up by the spaces described. It was a tempting view to take, that these spaces might be filled by gas alone, which, by the mechanical effect of pressure and by cutting off the fibres from their blood supply in the interstitial tissue, might lead to their speedy death. Attempts were made to prove this view correct by cutting thick frozen sections of fresh unfixed tissues, and looking for evidence of gas under the microscope, but none could be detected. On the other hand, in tissues fixed in corrosive sublimate, and more especially in material fixed by boiling before being embedded in paraffin, evidences of amorphous deposit in the spaces were found, which seemed to point to the contents being a fluid. In tissues fixed in formalin, from which the drawings were made, the spaces almost invariably appeared quite empty, and free from anything which stained. We therefore are of opinion that a toxic fluid, perhaps similar in constitution to the oedema which always accompanies gas gangrene to a greater or less extent, spreads along between the interstitial tissue and the fibres, killing off the latter as it advances. Once the fibres are killed, the anaërobic bacilli live on them practically as saprophytes, breaking down the sugars and producing abundant gas. This process is in strong contrast to what occurs in healthy muscle, where the presence of the organisms is without effect on the living fibres.

The rapid spread of the disease into living muscle can, we think, be explained on these lines. Fibres, each of which stretch without interruption for a considerable distance, are killed in the manner which has been described, and the dead tissue is then rapidly broken down and gas formed. The circle is a vicious one, for the toxic fluid which spreads between the fibres is no doubt formed in the gangrenous tissue behind, and so the condition spreads until the ends of the fibres are reached. This view also gives a satisfactory explanation of how single muscles may be found gangrenous, no spread having occurred to others close at hand. No opinion can yet be given as to the nature of the toxic fluid, which may either be a true bacterial toxin or something dependent on the breaking down of tissues.

Other points brought out by histological examination may now be referred to. With regard to the route followed by the organisms, these are, at the spreading edge, never found in the muscle fibres themselves, but are practically confined to the reticulum (Fig. XI). When the fibres are dead and being broken down, the bacilli invade the disintegrating fibres in numbers. At a later stage (Fig. XIII) all definite muscular structure becomes lost and gas is present abundantly between the remnants of the fibres. It is interesting to note that in muscle at this advanced stage of the disease the number of organisms appears much less than in the spreading zone. This is evidently partly due to many organisms staining badly, so that ghost forms are numerous. It seems probable that this stage, once reached, is inimical to the life of the bacilli, so that many are destroyed and disappear.

In rapidly spreading gas gangrene leucocytes are generally conspicuous by their absence in the muscular tissue involved (although they may be present in some number in the interfascicular planes). The mere speed of progression of the process in muscle may probably account for this, as a leucocytic reaction takes some time to develop. Where the spread of gas gangrene is being arrested in muscle, great leucocytic invasion is present. This is well shown in Fig. XII, taken from a muscle in an amputation stump. Here a recrudescence occurred in the stump, but was arrested after spreading a few inches only. Macroscopically a very definite pale zone was visible, and in section abundant phagocytosis of bacilli by polymorphonuclear leucocytes was found.

Control Experiments on Animals.

A considerable number of experiments have been carried out in animals to control the conclusions arrived at by the study of human tissues. Large rabbits were used, because

of their long hind legs, in which the spread of the disease could be watched at different stages. Gas gangrene being a disease of muscle, all the inoculations were made intramuscularly into the gastrocnemius or soleus. Several facts of considerable interest were brought out:

1. A spreading gas gangrene of the limb, quite comparable with the same disease in man, could be produced in rabbits, sometimes leading to a fatal result.

2. The surest method of inducing this result was by the injection of about one cubic centimetre of the fluid expressed from a human muscle showing fairly advanced gas gangrene. This fluid contained abundant bacilli, and all the products of tissue disintegration.

3. When the fluid obtained in this way was first passed through a Berkefeld V filter to remove the organisms, intramuscular injection led to marked local necrosis of muscle fibres, accompanied by considerable leucocytic reaction. No spreading oedema or separation of muscle fibres at all comparable with that described in human tissues could be brought about.

4. A rapidly spreading fatal gas gangrene was produced in one instance only by the injection of a pure culture of *B. perfringens* isolated in culture from a fulminating human case. In this experiment a haematoma of considerable size had been caused in the muscle at the site of inoculation, and this may have provided the dead tissue necessary to start the spreading disease. In tissues from this animal all the changes noted in the spreading margin of the disease in man were perfectly and completely reproduced. In some sections normal fibres were seen lying side by side with others of a deep eosin tint and separated off from the reticulum. At another place the appearances corresponded exactly with those shown in Fig. X, the sharpness and regularity of the interstitial network being very striking.

5. Other experiments carried out with pure cultures of *B. perfringens*, isolated from human cases, led only to a local gangrene at the seat of inoculation, round which a zone of granulation tissue quickly formed, completely walling off the damaged tissue.

CONCLUSIONS.

1. The rapidity of spread of gas gangrene into living voluntary muscle is so remarkable as to require explanation by a different process from that which governs ordinary septic invasion of tissues.

2. It is suggested that the facts are accounted for by the peculiar anatomical structure of muscular tissue. The sheaths enclosing the long individual fibres are so easily detachable as to form potential spaces into which toxic material can readily pass, causing necrosis of the fibres.

3. The early selective invasion of single muscles is consistent with the above view.

We wish to thank Colonel Cuthbert Wallace, C.M.G., consulting surgeon, for his help and interest in this work. The drawings from microscopic sections were made by Sergeant A. K. Maxwell, R.A.M.C., working under the auspices of the Medical Research Committee.

REFERENCES.

- ¹ Mullally and McNee, BRITISH MEDICAL JOURNAL, April 1st, 1916.
² Kenneth Taylor, *Lancet*, December 23rd, 1916.

THE SUCCESSFUL CONSERVATIVE TREATMENT OF EARLY GAS GANGRENE IN LIMBS BY THE RESECTION OF INFECTED MUSCLES.

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AMONG the points brought forward by Colonel Cuthbert Wallace in an article on gas gangrene¹ published in this JOURNAL some months ago were the following:

1. It is rare to meet gas gangrene without muscle injury.

2. It is chiefly a disease of muscles, and is rarely dangerous unless muscle is involved.

3. The lesion in its early stages may be described as a longitudinal one, running up and down the wounded muscles from the seat of the lesion. Muscles, or groups of muscles, are involved, while others escape.

4. It is rare to find all the muscles of a segment of a limb involved, save in a segment distal to one in which the main blood supply has been cut off. Thus the whole leg dies and becomes gaseous when the femoral artery has been blocked in the thigh.

5. There is little tendency for the infection to pass from one muscle to another. This is well shown in amputation stumps, where one muscle dies and becomes gaseous, while the rest of the cut muscles remain healthy.

From our own observations in clearing stations over a period ranging up to twenty-one months it is abundantly clear that these points cannot be controverted. In no case have we seen gas gangrene commencing as a subcutaneous infection; injured muscle is in all cases the initial focus, the appearance of crackling in the subcutaneous tissues being a secondary phenomenon, due to extravasation of gas from the infected muscles below.

RESECTION.

In view of this, it has been our aim to model our treatment on the following lines as soon as the condition is diagnosed: To explore the primary focus with a view to attempting to arrest the infection in the muscle, or group of muscles, involved by resection of the infected areas. Such resection may, as will be seen from the cases, involve a part or the whole of single muscles, or groups of muscles.

Resection should be limited to cases in which the main vessel of the limb is intact, and should be replaced by amputation where the operation must be so extensive as to be likely to give a limb which would be of less value than an artificial limb. Extensive resections, however, may be performed regardless of the ultimate utility of the limb as a life-saving operation, it having been quite clear in some of the cases recorded below that an amputation, as in Case XIII, or a further amputation, in Cases VII and IX, could not have been carried out without very grave risk to life. Resection should extend until muscle is reached which has the following characteristics:

1. The colour is unchanged.
2. The contractility is normal.
3. A good blood supply is present, as indicated by free bleeding from the cut surface.

Experience has shown that even if such muscles are, as they may be, slightly infected, free drainage and an open wound will arrest further development of the condition.

After-Treatment.

The treatment of cases after resection is carried out on the following lines: (1) The dressings are reduced to the absolute minimum—that is, one or two layers of gauze only are placed over the wound so as to allow free access of air and, if possible, sunshine to the wound region; (2) constant or intermittent irrigation of the wound by some modification of the Carrel method—eusol, saline, or hydrogen peroxide being used as the irrigating fluid.

In connexion with the cases described below, the point must be specially emphasized that gas gangrene had already developed in some patients, though they were admitted a very short time after being wounded. In fact, in units at the front established gas gangrene has to be treated *ab initio*, in addition to gas gangrene developing at a later stage.

We are indebted to Colonel Cuthbert Wallace, consulting surgeon to this army, for advice and assistance in the treatment of these cases, and to Captain J. W. McNee and Lieutenant J. S. Dunn, of No. 3 Mobile Laboratory, R.A.M.C., for the bacteriological and pathological investigations they have made in the cases.

CASE I.

Lieut. F., wounded 4 p.m. on November 2nd, 1916, by rifle grenade fragment; admitted at 7.15 p.m. the same day, that is, three and a quarter hours after being wounded.

When admitted he was clearly very ill, although he arrived as a walking case; his pulse was 120, of poor quality and irregular, his tongue was furred, and his features pinched and worn. There was an irregular wound the size of a threepenny-piece (that is, about 1.6 cm. in diameter) on the posterior aspect of the right arm just above the internal condyle of the humerus; there was no exit. The whole upper arm appeared