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ANAEROBIC CELLULITIS AND GAS GANGRENE

BY

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Infective gangrene in wounds is a subject of no little importance at present, and while our knowledge is yet far from adequate, enough facts have been established to render unnecessary some of the confusion which still exists regarding its diagnosis and treatment. Differences of opinion are greatest on the question of treatment, and there are wide divergencies in the results obtained from any individual method. These discrepancies are due in part to lack of differentiation between gas infection of the cellular connective tissues and true gas gangrene of muscle. A faulty diagnosis of gas gangrene is often made because attention is focused on the demonstration of gas or of gas-gangrene organisms in a wound instead of on the tissues in which the gas is produced, so that cures of gas gangrene are claimed as due to some particular treatment when in fact the condition was no more than a subcutaneous gas infection without involvement of muscle.

There are two stages in the diagnosis of a gas-infected wound: the first is the demonstration of gas, and the second the identification of the tissue involved. The demonstration of gas or of gas-gangrene organisms is easy and may be made by clinical, radiological, or bacteriological means; but the distinction between gas infection of the connective tissues and gas gangrene of muscle is more difficult and far more important, and can be made only on clinical grounds, radiology and bacteriology playing no part.

Three groups of cases occur; in these the organisms of infective gangrene may be found in a wound (1) as harmless saprophytes in ulcers, with no pathogenicity; (2) as pathogenic organisms producing an infection of the cellular connective tissues—gas infection of a wound or anaerobic cellulitis; or (3) as invaders of muscle—true gas gangrene.

1. Saprophytic Anaerobes

Numerous observers have described the saprophytic form of gas-gangrene organisms. Thus Fleming in 1915 found *Cl. welchii* in 127 out of 210 war wounds of varying ages; Manson (1932) found gas-producing anaerobes in 11 out of 32 chronic ulcers of the limbs; and Roberts, Johnson, and Bruckner (1933) found clostridia in 21.7% cases of unprepared abdominal skin, on 8.5% of surgical knife blades, and from the peritoneum in as many as 14.2% cases operated on for non-inflammatory conditions. Saprophytes of this type are capable of producing toxins: Muriel Robertson (1941) found highly toxic types of *Cl. welchii* in recent wounds, their presence in which had caused no symptoms. The bacteriological demonstration of gas-gangrene organisms in a wound has therefore little surgical significance.

2. Anaerobic Cellulitis

Gas infection of a wound without gangrene of muscle is probably the commonest clinical type of active infection

by the gas-producing anaerobes. In this condition gas is produced in the wound, which may be demonstrated both clinically and radiologically; but there is no infection of muscle, and the patient may well recover without any active treatment. It is certain that many of these cases have been described as gas gangrene and reported as having been cured by different methods of treatment.

The site of the infection is the cellular connective tissues, and therefore there is no reason why the condition should not be recognized by the term "anaerobic cellulitis," comparable to other forms of cellulitis such as the streptococcal type. Following compound injury, and quite apart from muscle damage, conditions in the subcutaneous tissues may favour the growth of anaerobic organisms, with gas production from the proteins and carbohydrates in these tissues and from associated haematomata. This anaerobic cellulitis may spread in the fascial planes for some distance, but in the absence of a suitable pabulum of damaged muscle the infection may remain superficial or completely resolve when the supply of connective-tissue media is exhausted or when anaerobic conditions are terminated by suitable surgical incisions. An important feature in such cases is that the musty odour typical of gas gangrene is not present; this is probably to be correlated with the absence of muscle necrosis. With this local growth of anaerobes toxins are no doubt produced, and the patient suffers from a toxæmia of varying severity, depending on the extent of the damaged tissues and the nature and virulence of the organisms.

This condition is the one referred to usually as "local gas gangrene," but in the absence of muscle infection it would be preferable to distinguish it as "anaerobic cellulitis," particularly because its prognosis and treatment are so different from those of gas gangrene. Obviously the local treatment need never be drastic; if one can be certain that the condition is no more than a cellulitis, there is no necessity for radical surgery. Adequate treatment consists in removing skin stitches and opening up the wound or, in a more extensive case, making incisions under an anaesthetic. In addition, serotherapy and chemotherapy must be instituted, partly to mitigate toxæmia and also because they may help to arrest spread of the infection to muscle or of impaired vitality, should any be present in the wound.

The following are three cases of anaerobic cellulitis:

Case 1.—Male aged 30. Road accident, 4/11/38. Multiple abrasions and contusions of lower limbs, with a puncture wound just above the left knee. Given 1,000 units of A.T.S. and 4,000 units of polyvalent anti-gas-gangrene serum. Operation two hours later showed only a large subcutaneous haematoma of the left thigh, and the wound was excised and sutured. On the fourth day there were signs of a gas infection, with crepitus and gas bubbles in the wound. The general condition was fairly

good. T. 101°, P. 108. Under general anaesthesia the wound was opened up and the infection was found to involve only the subcutaneous tissues. It was left open, with hydrogen peroxide dressings, and the infection soon resolved, the temperature becoming normal in three days. Culture of the wound exudate showed *Cl. welchii*.

Case 2.—Female aged 19. Road accident, 28/9/38. Multiple abrasions and lacerations of lower limbs and right hand. Given 1,000 units A.T.S.; wounds excised and sutured. The laceration of the right foot involved the incomplete avulsion of a large piece of skin of the dorsum with considerable soiling by road dirt. Next day the patient was ill. T. 101°, P. 134. Given 10,000 units of anti-gas-gangrene serum and 2 grammes of sulphanimide t.i.d. A few stitches were removed from the wound of the right foot, when a little odourless brownish fluid escaped. The pulse remained 120-130 until the next day, when there were crepitus and gas bubbles in the wound. A further 20,000 units of anti-gas-gangrene serum was given. Culture of the wound exudate showed *Cl. welchii*. The general condition improved on the third day; there was no spread of the gas infection, and the wound suppurated and eventually developed a clean granulating surface.

Case 3.—Male aged 45. Air-raid casualty, 9/11/40. Compound fractures of left femur and left hand and perforating wound of left leg. Given 3,000 units A.T.S. Excision of wounds and packing with vaselined gauze four hours after injury. The wound of the left leg consisted of a penetrating track through the gastrocnemius; the limb was immobilized with skeletal traction. Immediately after operation he received 10,000 units anti-gas-gangrene serum and 2 grammes of sulphapyridine intramuscularly, the latter being continued as 1 gramme four-hourly. The following day, twenty-four hours after injury, the general condition was fair; T. 99°, P. 120. There was discoloration of the skin of the antero-lateral surface of the left leg just below the wound, with crepitus in this area, and a radiograph showed the presence of gas. There was a mild odour of stale blood in the wound, but no suggestion of the mouse-like smell of gas gangrene. Culture of the exudate showed *Cl. welchii*. Anti-gas-gangrene serum was given, a total of 150,000 units being injected during the next twenty-four hours in doses of 10,000 and 20,000 units at two-hourly intervals into the left thigh and upper end of the leg above the wound. Crepitus disappeared after twenty-four hours, and the wounds suppurated. The Hb on the fifth day was 50%, with 15,700 white cells per c.mm. The fracture united well and the wounds healed within fourteen weeks.

3. Gas Gangrene

The term "gas gangrene" should be reserved for the type of case in which there is gas production with necrosis of muscle. Its prognosis and treatment are different from those in anaerobic cellulitis, and failure to make this distinction is almost certainly the principal reason for the inconsistency of the results reported from various individual methods of treatment, particularly by x rays. While in every wound with anaerobic gas infection we should suspect gas gangrene and watch closely for it, it is unjustifiable to label every case as such unless or until it is established that there is muscle necrosis. It is of interest to note that the earlier clinical descriptions made this distinction clear, whereas more recent writers seem to neglect the point. Thus Fraser (1919), in discussing the types of anaerobic wound infection, clearly recognized anaerobic gas infection of the wound and gas gangrene of muscle, and Keen (1918) also regarded the distinction as of importance. More recently Hosford (1940) and Jocelyn Swan (1940) have called attention to it, and Tudor Edwards (1940) similarly emphasizes the difference between the two conditions.

Diagnosis of gas gangrene resolves itself therefore into the collation of evidence of necrosis of muscle, and the value of any signs and symptoms must be considered with reference to their use in this respect. These are: (a) general signs; (b) local signs; (c) clinical symptoms and signs; (d) inspection of muscle.

GENERAL SIGNS

The toxæmia of an established case of gas gangrene is of course severe, and a gas-infected wound in an extremely ill patient is almost certainly the site of infective necrosis of muscle. But in anaerobic cellulitis without muscle damage there is also a toxæmia, difficult to distinguish from early gas gangrene: it is after all merely a question of degree of toxæmia, since the organisms and toxins may be identical. All three cases of anaerobic cellulitis described above showed toxæmia, particularly Case 2, with raised temperature and pulse rate. Furthermore, it is often difficult to make an exact clinical estimate of the severity of a toxæmia. Again, the signs suggestive of gas-gangrene toxæmia, particularly the raised pulse rate, may be due to shock following the injury, primary haemorrhage, operation, or associated injuries. There are no constitutional symptoms or signs which are absolutely diagnostic of muscle necrosis.

LOCAL SIGNS

(a) *Bacteriology.*—The finding of anaerobic organisms does not give any information about the involvement of muscle.

(b) *Radiology.*—The demonstration of gas in a radiograph does not prove that this is being produced by disorganization of muscle. In Case 3 the radiograph showed gas, but there was never any clinical evidence of gas gangrene, and the gas was no doubt in the connective tissues. The use of radiography has been well summed up by Ogilvie (1940): "X-rays will disclose gas in the tissue planes, but the method is not particularly helpful, since the discovery of gas and the diagnosis of gas gangrene are two different things. The use of x-rays in diagnosis refers to gas infection rather than gas gangrene. If a case is not clinically one of gas gangrene the discovery of gas in a film will not make it so; if it is, photography is a waste of time."

CLINICAL SYMPTOMS AND SIGNS

Pain.—The complaint of pain in the presence of a gas-infected wound is suggestive of muscle involvement, but it is not always a symptom, and only one of the four cases described below had pain of any severity.

Odour.—This is one of the most important clinical signs, because it is probably due directly to the breaking down of muscle tissue as distinct from the connective tissues. The odour of gas gangrene is distinct; it is a musty or mouse-like smell quite different from the odour of stale blood which occurs in a discharging wound a few days old, such as is associated with anaerobic cellulitis. Unfortunately the actual chemistry of the odour is unknown; it would be valuable to have biochemical proof that the gas is formed from the protein or carbohydrates of muscle tissue. But clinical experience very strongly suggests that this particular gas emanates from the action of anaerobes on muscle and on no other tissue. If it is agreed that the breakdown of muscle alone gives rise to this particular odour, then this is the only sign (apart from direct inspection of the muscle) that is pathognomonic of gas gangrene as compared with anaerobic cellulitis. It is certainly a fact that, in spite of numerous other suggestive signs, the experienced surgeon when asked to see a doubtful case will base his diagnosis almost solely on the local clinical inspection of the wound, with particular reference to the odour. Thus Ashurst (1929) says that in the Second Battle of the Marne it became his habit "to wander around the corridors and smell the patients. Those that smelled like mice were operated on right away because they had gas gangrene. The rest of them could wait awhile."

In the present lack of knowledge of the exact nature and cause of the odour, the most that can be said is that it is probably the result of the action of one or more individual anaerobes on muscle tissue and that it is present in most cases of gas gangrene. Since infective gangrene may be due to a variety of organisms, it is not to be expected that all cases will have the characteristic odour, or even that all cases will have gas. Cases of infective gangrene in wounds without gas production have been described: Ghormley (1935) described one such case in which *Cl. septicum* was identified. This type of case is unusual; undoubtedly in the vast majority of cases of infective gangrene of muscle there is gas production with the characteristic odour.

INSPECTION OF MUSCLE

This of course provides the most valuable evidence, but involves operation. Diagnosis is always confirmed thus and the extent of the lesion is determined. The gross features are well recognized and will not be described. The criteria of viability of muscle have been well summarized by Ghormley (1935) as: "If the muscle is red it may be viable; if it contracts when pinched it is usually viable; if it bleeds freely it is probably viable."

The diagnosis of gas gangrene is therefore essentially a clinical one, and depends mostly on the local signs, of which the most important is the odour. It is probably the experience of many that more cases are diagnosed in the early stages by the inspection of a wound as a deliberate routine rather than as the result of a suggestive temperature chart. It follows that a four- or six-hourly examination of the wound should be the practice in the immediate post-operative period in cases in which gas gangrene is a likely complication.

Clinical Types of Gas Gangrene

The commonly recognized types are: (1) local, (2) single muscle, (3) group of muscles, (4) segment of a limb, (5) fulminating.

It is suggested that this classification does not emphasize the important distinction between the first type, "local gas gangrene," and *all* the others. "Local gas gangrene" is really a cellulitis, not involving muscle, and it should be separate from the others, which differ among themselves only in degree: (1) Anaerobic cellulitis (so-called "local gas gangrene"); (2) Gas gangrene: (i) single muscle, (ii) group of muscles, (iii) segment of a limb, (iv) fulminating. This is not an academic distinction; its recognition would help to avoid confusion in diagnosis, in treatment, and, perhaps as important as anything, in the evaluation of methods of treatment.

Predisposing Factors in Gas Gangrene

In a wound contaminated with suitable anaerobes there must be factors which determine the infection of muscle as distinct from the connective tissues. These factors may be: (1) Variations in virulence of the organisms. (2) Suitable conditions for growth of organisms: (a) anaerobic conditions; (b) damaged muscle.

Variations in Virulence.—It is a well-known bacteriological fact that organisms vary in toxicity and invasiveness. It may be important in gangrene, but in any case it is a subject about which very little can be done in a practical way.

Suitable Conditions.—According to Eliason, Erb, and Gilbert (1937), "the important single factor in the production of gas gangrene is not contamination with the organism

per se but rather a suitable soil in which it can grow." The essential medium is well recognized to be damaged muscle, and it may be effective in any particular case in one or more of three ways: (i) direct trauma to muscle; (ii) impaired blood supply; (iii) delayed excision. It is not necessary to go further into these well-established points, of which the three cases described below are illustrative.*

Case 4.—Male aged 42. A.R.C., 8/10/40. Antero-posterior perforating wound of upper third of left thigh and a small laceration 3 inches long on the lateral side of left calf. Operation seven and a half hours after injury showed a large haematoma due to a puncture wound of the upper third of the femoral artery, which was ligated. The leg wound showed bruising of a few fibres of the gastrocnemius. The wounds were excised and packed with flavine gauze, and sulphapyridine therapy was instituted. Post-operatively there was no pain in the leg, but inspection thirty hours after injury showed discoloration around the leg wound, with crepitus and the typical musty odour of gas gangrene. Amputation through the lower third of the thigh was performed, and subsequent progress was good. The two important predisposing factors in this case no doubt were the damaged femoral artery and delayed operation, the diminution of blood supply being sufficient to determine the rapid onset of gas gangrene in the presence of infection even in such a trivial muscle injury.

Case 5.—Male aged 26. A.R.C., 8/10/40. Multiple small lacerations of face, chest, right arm and forearm, and both legs. Operation eight hours after injury. There was a laceration 4 inches long on the back of the left leg, with some muscle damage, which was excised and sutured, with drainage. The numerous other wounds were excised, exploration of the right arm showing a complete division of the brachial artery. Post-operative sulphapyridine and anti-gas-gangrene serum therapy was instituted. Gas gangrene developed in the left leg fifty-four hours after injury, by which time he had been given 10 grammes of sulphapyridine and 80,000 units of anti-gas-gangrene serum. Amputation through the lower third of the left thigh was performed, and the subsequent progress was satisfactory. The right forearm developed some muscle necrosis and dry gangrene of the tips of the second, third, and fourth digits. The wound in the leg giving rise to gas gangrene was small, and the deciding factor in the case must have been its delayed local treatment.

Case 6.—Male aged 59. Railway accident, 18/4/40. Compound dislocation of right ankle-joint, with severely crushed foot, and compound fractures of upper thirds of left tibia and fibula, with considerable laceration of the calf muscles. General condition poor throughout. After two hours the left leg, which was attached only by nerves and a few muscle fibres, was removed in the patient's bed under local novocain and the stump packed with flavine gauze. Operation five hours later, the amputation stump being excised and the right foot amputated through the ankle-joint, the wounds being packed with flavine gauze; 3,000 units of anti-gas-gangrene serum given. Gas gangrene developed in the left thigh seventeen hours after injury, and the patient rapidly became delirious, dying ten hours later. The wound exudate contained *Cl. welchii* and other organisms in great numbers.

Prophylaxis of Gas Gangrene

Excision of Wound.—It is well recognized that the one almost certain way of avoiding gas gangrene is by immediate and complete excision of damaged tissue, especially muscle. The importance of the time factor should be emphasized. Actual practice, of course, may fall short of these desiderata owing to such things as the nature or severity of the injury or to the delay incurred in resuscitation from shock, in transport, or in arranging operation; so that it is important to promote other means of prevention, it being always understood that they are supplementary

* Cases 4, 5, and 7 have already been described in the *British Medical Journal* (1941, 1, 273).

to, and not substitutes for, excision. In advocating the use of serum, Bates (1937) says: "Prophylactic serum without intelligent surgery cannot be expected to prevent the development of gas gangrene."

Sulphonamides.—Experimental evidence strongly supports the use of sulphonamides in prophylaxis. Thus Stephenson and Ross (1940) found that sulphanilamide and sulphapyridine protected mice from lethal doses of *Cl. welchii* and *Cl. septique*, sulphapyridine being more potent, although they were of no use against *Cl. oedematiens*. The best results were obtained from the combined use of sulphapyridine and serum therapy. Hawking (1941) has similarly obtained good results in guinea-pigs, the most effective drug being sulphathiazole, and the best route the local application. His results also showed the importance of immediate treatment, a delay of two hours considerably reducing its value and six hours rendering it useless. There is not yet enough material available to estimate the prophylactic value of the sulphonamides in gas gangrene clinically, but it is to be hoped that the results may support the experimental evidence. It is probably best to give sulphonamides both internally and locally in the wound, and it may even be wise to institute such treatment from the time of admission of the patient, before operation. Considering the rapid onset of gas gangrene, which under suitable conditions may well be from the moment of injury, it is likely that immediate local administration is the most important of all methods. Gordon Watson (personal communication) recommends the application of as much as 40 grammes of sulphanilamide to the wound. In the following case gas gangrene developed in an amputation stump in spite of the administration of a standard prophylactic dose of sulphapyridine given by intramuscular injection (8 grammes): no local application of the drug had been made.

Case 7.—Female aged 16. A.R.C., 8/10/40. Compound fracture of upper thirds of left tibia and fibula. Amputation through the lower third of the thigh, performed two and a half hours after injury, with closure and drainage. Post-operative sulphapyridine therapy instituted. Gas gangrene developed in the stump thirty-six hours after injury, the patient having had 8 grammes of sulphapyridine but no anti-gas-gangrene serum. The wound was opened up and irrigated with hydrogen peroxide, and 40,000 units of anti-gas-gangrene serum were given, but the patient died in seven hours.

Antisera.—Opinion is divided about the use of antitoxic and anti-bacterial sera. Experimentally, good results have been obtained by the combined use of serum and sulphonamides (Stephenson and Ross, 1940). Henderson and Gorer (1940) found that in mice the best effects were obtained by the combined action of sulphapyridine and antitoxin, or of sulphapyridine and anti-bacterial serum, against infections by *Cl. septique* and *Cl. welchii*. It seems that the use of serum in addition to the sulphonamides is advisable. It is probably best given both intramuscularly around the wound and intravenously. Case 3, which developed a *Cl. welchii* infection that remained localized as a cellulitis, was treated by repeated local intramuscular injections of serum.

Adequate prophylaxis should therefore probably comprise: complete and immediate excision of the wound; administration of sulphonamides, particularly local application; injection of antisera, especially intramuscularly around the wound.

Treatment of Gas Gangrene

Successful results in the treatment of gas gangrene have been recorded with methods varying from the most conservative, such as x-ray therapy, to the most drastic, such as

amputation, and the unbiased critic must find it difficult to believe that one disease could call for such widely differing treatments. Thus while amputation is carried out as a life-saving procedure by some, others condemn this measure under any circumstances, as, for example, Kelly and Dowell (1936), who, in recommending x-ray treatment, say: "Since there is so much shock connected with amputation, and, furthermore, since the diseased area is not all eliminated by some of these amputations, it again seems worth while to omit amputations as an obsolete therapeutic procedure for gas bacillus infection."

Obviously, either many unnecessary operations are being performed or conservative treatment is being applied to a different class of case. Almost certainly the latter is a true explanation of these apparent discrepancies in the results of treatment, and results of numerous cases of anaerobic cellulitis have probably been reported as cures of gas gangrene by conservative means. It is essential to be certain that the case is not simply one of cellulitis before being satisfied that a particular treatment has successfully overcome gas gangrene.

The various forms of treatment are local excision and amputation, sulphonamides, antisera, and x rays.

Excision.—There is no doubt that if infective necrosis of muscle is present the only sure way of dealing with it is by adequate excision. If it is localized to one muscle or muscle group, these may be removed; if it is more extensive, involving a segment or more of a limb, amputation is called for.

Sulphonamides.—As in prophylaxis, there is every reason to use these drugs as a local application as well as by general administration. Again, their use does not dispense with adequate surgical excision. Bohlman (1937) reported three cases of gas gangrene which recovered after sulphanilamide therapy, and Jocelyn Swan (1940) recorded two successful cases following sulphonamide treatment in addition to surgery.

Antisera.—Bates (1937) reported 16 cases treated without serum in which the mortality was 50%, and 16 cases in which serum was used, with a mortality of 18%. Larson and Pulford (1930) reported 6 successful results in 7 cases treated with anti-gas-gangrene serum, the injections being made intramuscularly locally around the wound as well as intravenously. It is probably advisable to use antisera in this way in all cases.

X Rays.—Cases of success from x-ray treatment have been reported—e.g., by Kelly and Dowell in 1936. While it is impossible to be certain, it is very probable that the type of case which recovers with x-ray treatment is not true gas gangrene but anaerobic cellulitis. If, for example, Cases 1, 2, and 3 above were to be loosely called "local gas gangrene" they might be regarded as cures of gas gangrene due to any particular treatment that was given. It is essential in evaluating treatment to be certain of the presence or absence of muscle infection, and not to use the term "gas gangrene" unless muscle necrosis is present.

Summary

It is suggested that more care should be given in distinguishing between gas infections of the cellular connective tissues and true gas gangrene, and that the term "anaerobic cellulitis" should be used to describe the former.

Gas infections of wounds should be classified as: (1) anaerobic cellulitis (so-called "local gas gangrene"); (2) gas gangrene—(i) single muscle, (ii) group of muscles, (iii) segment of a limb, (iv) fulminating.

The importance of this distinction is in diagnosis, treatment, and evaluation of treatment. It is suggested that inclusion of all

varieties of gas infection of wounds as gas gangrene has been responsible for considerable diversity of opinion on the value of different methods of treatment.

The differentiation is essentially a clinical one, and the importance of odour as a sign of gas gangrene is stressed.

The histories are given of three cases of anaerobic cellulitis and four cases of gas gangrene.

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FURTHER OBSERVATIONS ON ANTI-SEPTIC SNUFFS

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In continuation of the work previously described (Delafield *et al.*, 1941) some further observations on the effect of antiseptic snuffs on nasal carriers of staphylococci and other organisms are now presented. Seventeen of the subjects who provided the material for the earlier report have been further examined for twenty weeks—from early January to the middle of May. Nasal swabs, one from each nostril, were taken as before on three consecutive days each week and the technique of examination was in every respect identical with that previously described.

The Antiseptic Snuffs Tested

The snuffs which were the chief subjects of study had the following composition:

Sulphathiazole Snuffs:

- (a) 10 parts by weight of sulphathiazole
90 " " " " " magnesium carbonate
- (b) 33.3 parts by weight of sulphathiazole
66.6 " " " " " magnesium carbonate
- (c) 50 parts by weight of sulphathiazole
50 " " " " " sulphapyridine

Control Snuff:

- (d) Light magnesium carbonate.

To these 1% of menthol may be added according to individual taste. If children are to be treated it would probably be best to omit the menthol. The general impression obtained is that (b) and (c) are better than (a), but that (b) and (c) are equally effective.

The use of lycopodium powder was discontinued, as two of the subjects showed signs of apparent sensitization after a week or two. These signs—profuse rhinorrhoea and headache—disappeared when magnesium carbonate was substituted for the lycopodium. Dr. M. H. V. Cameron

(1941) directed attention to the possible danger of the lycopodium producing granulomata, and cited papers on this subject by Erb (1935) and McCormick and Ramsey (1941). Dr. Cameron is also of the opinion that magnesium carbonate might be a danger, as granulomata apparently due to the use of magnesium silicate have been described. It is probable, however, that when this reaction occurs it is not due to the magnesium ion but to the silicate ion.

Penicillin (1% in lycopodium powder), which had previously proved effective with the few subjects on whom it had been tried, was again tested at the same concentration but with magnesium carbonate powder as a diluent. In this form the penicillin was much less effective than it had previously been, and *in vitro* tests showed that in a few days the snuff lost its power to inhibit the growth of staphylococci. Prof. Florey states that penicillin is rapidly destroyed in an alkaline medium, and it is probable that there is a sufficiently destructive alkalinity on the surface of the particles of magnesium carbonate. Before the use of lycopodium was discontinued penicillin (1%) associated with sulphathiazole (33.3%) and lycopodium was tested on a few subjects, but was found to be no more effective than the sulphathiazole snuff alone.

Method of Taking the Snuff

The subjects have taken the snuff six times a day, either by the classic method or by sniffing it from one corner of a small folded triangular piece of paper. The amounts thus taken per day have been weighed. Twelve pinches or a day's supply of the sulphathiazole (33.3%) in magnesium carbonate weigh 0.075 gramme, representing an intake of less than 0.6 gramme of sulphathiazole a week. Similarly a week's intake of the sulphathiazole-sulphapyridine snuff weighs about 1.6 grammes. No toxic symptoms were ever observed, even after many weeks of snuff-taking.

Persistence of Snuff in the Nose

Study was made of the amount of sulphathiazole taken up by a nasal swab. Swabs from both nostrils of the 17 subjects were examined chemically about two hours after the last snuff-taking. In 11 out of 34 swabs sulphathiazole was demonstrated in amounts ranging from 0.03 to 0.39 mg. As the presence of the drug on the nasal swab might affect the bacteriological findings, all subjects were directed not to take any snuff during the twelve hours preceding swabbing, which was carried out at 10.30 a.m. After this instruction no sulphathiazole was demonstrated on the nasal swabs.

Results with Nasal Carriers of Staphylococci

All the 17 subjects under test were carriers of staphylococci: 3 were light but persistent carriers, whereas swabs from 14 yielded heavy growths of *Staph. aureus* or a coagulase-positive *Staph. albus*. These organisms were sometimes found together on the same plate.

In all cases except one the staphylococci were very greatly reduced as a result of treatment with sulphathiazole snuff, but they never entirely disappeared. Only one carrier was relatively resistant to the snuff in that the number of organisms found was but slightly reduced. In general, when the number of colonies found was small as a result of treatment the staphylococci were white and coagulase-negative, although small numbers of coagulase-positive white staphylococci and of *Staph. aureus* tended to persist in a few carriers. No carrier was definitely "cured." Two to three weeks after treatment was stopped heavy growths of *Staph. aureus* and coagulase-positive *Staph. albus* were again obtained. In a few instances the organism did not appear in profusion until between four and six weeks had elapsed.