A Report

UPON 25 CASES OF
ACTINOMYCOSIS,WITH ESPECIAL REFERENCE TO VACCINE
THERAPY.A DISCUSSION OF SOME PROBLEMS CONNECTED WITH
THE DISEASE.

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In a previous communication¹ I have described the mycelial and other micro-organisms met with in investigating a series of cases of human actinomycosis, most of which were under treatment at the Inoculation Department, St. Mary's Hospital, during the years 1911-15. A clinical account of several of the cases has already been published by Mr. V. Z. Cope,² who originally sent them to the Inoculation Department and afterwards collaborated with Sir Almroth Wright in the direction of their treatment. (Mr. Cope's paper also gives a valuable clinical account of the actinomycotic infections in general.)

In the present communication it is proposed to record what was learned from this series of cases in respect of the diagnosis, the clinical course, and particularly the treatment of the disease; and subsequently to discuss two questions which arise—viz., What is the source of these infections? and What restrictions is it advisable to put upon the use of the term actinomycosis?

Definition.—The cases here dealt with all presented granulomatous lesions from which the so-called "sulphur granules," visible to the naked eye, were forthcoming, and these granules were in every case composed of a feltwork of Gram-staining mycelium. The importance of strictly limiting the use of the terms actinomycosis (and paractinomycosis) to cases of this kind will be discussed later.

Diagnosis.—We have at present no reliable method of detecting an actinomycotic infection in its early stages—i.e., prior to the occurrence of suppuration. The slowly progressive, comparatively painless, and indurated lesion may suggest the diagnosis, but one is at a loss to confirm it by blood examinations, for opsonic estimations will often fail to distinguish between a tuberculous and an actinomycotic infection (the opsonic power to the tubercle bacillus is frequently high in actinomycosis), and agglutination tests with actinomycetes, although they will usually give positive results in advanced cases, are apt to be negative in the milder cases. Further observations on this latter point are required.

Of the 25 patients now under review almost all came to the hospital with lesions actually discharging or with an abscess ready to be evacuated. In such circumstances the diagnosis need never be long in doubt. All that is then required is to detect the "sulphur granules" in the pus and to determine their mycelial structure. A little experience of these granules enables one very readily to recognise them, either as the pus is evacuated or lying free on the granulations at the mouth of a sinus.

A word of warning may not be out of place here. Cases of actinomycosis are not infrequently missed, I think, because the surgeon does not himself search for granules in the fresh pus, but simply directs a specimen to be sent to the laboratory. Pending its examination the pus clots and the granules, being caught up in the coagulum, become more difficult to detect. Moreover, the pathologist, often not forewarned that the nature of the case suggests the possibility of actinomycotic infection, does not search for a granule, but takes a loopful of pus at random for film preparations and the inoculation of culture medium. Unless he has the good fortune (a somewhat rare occurrence) to include a

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commencing colony of actinomycetes in such a random sample of pus he is very unlikely to find any filaments of that organism, for these, by reason of their habit of growth in conglomerate masses, do not become disseminated through the pus.

The following simple procedure may be recommended for the detection of granules whenever their presence is in doubt. A few drops of pus are collected in a test-tube half full of water and fitted with a cork. On vigorously shaking the tube all the elements of ordinary pus will be emulsified or at least reduced to fine shreds; if, however, actinomycotic granules are present they will not be broken up, and on holding the tube up to a light will be easily detected by virtue of their opacity as cream-coloured spherical bodies of about $\frac{1}{2}$ to 1 mm. diameter, which quickly sink to the bottom of the fluid.

With the finding of granules a provisional diagnosis of actinomycosis can be made. For confirmation of the diagnosis it remains to verify the presumption that these granules are composed of Gram-staining mycelial elements, and, whenever possible, to identify the organism by isolating it in pure culture. For these purposes the granules are transferred as required by means of a capillary pipette to the surface of a microscopic slide. Lightly crushed under a cover-glass and examined unstained with a low power objective, the characteristic "ray" formation of clubs will be seen between an outer shell of massed leucocytes and the inner core of the granule. The "rays" form, in fact, the whole periphery of this core. On crushing further and staining the films obtained by sliding the cover-slip off the slide the core itself is seen to be composed of a tangle of the filaments of actinomycetes. These filaments retain Gram's stain, but somewhat irregularly. The further procedures necessary for obtaining cultures—and the characters by which a given organism may be identified with *Actinomyces bovis*—are described in the author's earlier paper.¹

THE INCIDENCE OF THE DISEASE AND ITS ULTIMATE
ISSUE.

There is reason to think that actinomycosis occurs more frequently in this country than is generally supposed. In the cases which end fatally a correct bacteriological diagnosis is often made only when the disease is far advanced, or post-mortem, and it therefore appears probable that a large number of the less severe cases escape recognition altogether—notably those cases in which the infection is situated about the lower jaw, and possibly also, as Mr. Slesinger³ has suggested, some of those in which the vermiform appendix is affected. In Table I. the patients observed by the author are divided up according to the site of their infection; the incidence in the two sexes is also shown, and the ultimate issue of the disease.

TABLE I.

Site of infection.	No. of cases.	Males.	Females.	Ultimate result.
Face or neck ...	10	7	3	9 recovered completely; 1 died.*
Thorax ...	8	5	3	7 died; 1 lost sight of.
Abdomen... ..	6	1	5	5 died; 1 recovered.
Dorsum of hand	1	1	—	Recovered completely.
Total	25	14	11	—

* Death was due to cerebral abscess, resulting from direct extension of the disease through the skull.

Table I. confirms the usual experience that (a) cervico-facial infections are the most numerous and also the most likely to recover; (b) infections of the thorax and abdomen are usually fatal. The latter conclusion should perhaps be stated with some reserve, for the future may show that actinomycotic infections of the vermiform appendix occur much more commonly than has been supposed, and that many such cases are promptly cured by the ordinary operation of appendicectomy. (Slesinger.³)

Age of the cases.—Seventeen of the 28 cases were young adults, 7 were older subjects (one of them being 70 years of age), and 4 were children between the ages of 10 and 13. I have not known the disease to occur below the age of 9.

Duration of the disease.—The course of these infections was commonly a very slow one. The disease had usually been in progress for several months before the patients came to the hospital for treatment, and although in three or four instances cure was obtained within a few weeks, the larger number of those who recovered were under treatment for a period of months. One case in whom the infection extended widely in the ramus of the mandible was apparently cured after three to four years, but a small focus reappeared in front of the ear and has persisted for a further two years. The fatal cases of thoracic or abdominal infection usually survived from one to two years from the onset of the disease. One abdominal case was terminated abruptly after several weeks in hospital by the development of septic peritonitis.

THE TISSUES AFFECTED BY THE DISEASE.

The outstanding feature of the pathological process in all the cases has been the extension by direct erosion of contiguous tissues—particularly connective tissues. Such extension has usually been accompanied by a deep induration, often quite a “wooden” induration over a considerable area around. Although the opportunity has not occurred to prove it by microscopical examination, one may, I think, surmise that this induration extends far beyond the area actually invaded by the actinomyces, for frequently, when a central abscess cavity has been evacuated, the indurated tissues promptly regained their normal softness. (It may be noted here, in passing, that no one has, so far as I am aware, succeeded in reproducing an actinomycotic lesion which has these two characteristics—progressive erosion of connective tissues and “wooden” induration—in any of the ordinary laboratory animals.)

The process of erosion has not involved the skin except in the immediate neighbourhood of sinus openings. In some cases, however, a considerable area of skin has been undermined by the spread of the disease in the subcutaneous connective tissue. The mucous membranes also seemed to be comparatively immune. It is a remarkable and, as yet, an unexplained fact that in the cervico-facial cases, although the infection presumably occurs from within the mouth or pharynx, the suppurative process almost always develops outwards towards the skin and seldom points in the mouth. None of the ten cervico-facial cases presented any evidence of the disease in the mouth when seen by the author, but three of them gave a history which pointed to its probable commencement in that situation. In one case the tonsil was incised at the first visit to the hospital, in another case a tooth was removed for an alveolar abscess, and in the third “incisions were made both inside and outside the mouth.”

The involvement of bone, as judged by ante-mortem observations, has been exceptional rather than usual. Very possibly post-mortem examinations of the fatal thoracic and abdominal cases would have told a different tale. In one case (No. 6 of Mr. Cope's series²) the mandible was extensively tunnelled by little canals lined with granulation tissue, and much new bone formation—particularly of the outer lamella—had occurred. The periosteum was involved in a dense, fibrous, almost avascular tumour. This was the only case in which the changes in bone constituted a notable feature. In several other cases bones adjacent to an actinomycotic infection of the soft parts were eroded and sometimes perforated by it in the course of the disease, but in every instance this involvement was apparently limited to a small area. The ribs and sternum, the ileum and the temporal bone were affected in this way.

The remarkable immunity of the lymphatic glands in this disease, which has frequently been noted by other observers, was again evidenced in this series of cases.

I do not remember having seen these glands affected in any case during life, and in one abdominal case which was examined post mortem, although the disease had spread widely, the mesenteric glands were quite unaffected.

TREATMENT.

Most of the cases had been treated by potassium iodide and by incisions before coming to the Inoculation Department at St. Mary's Hospital. The iodide had not usually been pushed beyond 30–40 gr. per diem; in one or two instances 60–90 gr. had been given. In these doses the drug had not exercised any appreciable effect upon the disease. Its use was usually discontinued soon after the patients came under observation; in a few instances, however, on the suggestion of the surgeon who was collaborating in the treatment of a patient, the drug was continued and pushed up to 180 gr. or more per diem, but still without effecting any improvement in the patient's condition. It should be acknowledged that the patients so treated were very unfavourable cases.

Upon inquiring into the origin and the general experience of this method of treatment I have failed to find that it has an assured scientific basis, or even a sufficient vindication by results. Introduced empirically by Thomassen⁴ in 1885 for actinomycosis of the tongue in cattle, it was later acclaimed by Nocard⁵ (1893) as an almost infallible remedy for this condition. When it came to be applied to the treatment of other actinomycotic lesions in cattle the results seem to have been less uniformly good, but I understand that it is still regarded by the veterinarians as a specific remedy.

Investigations undertaken with a view to finding an explanation of its reputed specific action have so far been quite unsuccessful. The organism does not lend itself readily to the demonstration of bactericidal effects, but observations have been made by Harbitz and Grondahl⁶ on the growth obtained when potassium iodide was incorporated in various culture media. They concluded that *Actinomyces bovis* was but little affected by the presence of iodide in concentrations of from 0.25 to 2 per cent.

At St. Mary's Hospital we have approached the problem from a different point of view. It occurred to Captain S. R. Douglas that the resolution of syphilitic gummata under treatment with iodide might perhaps depend upon a reduction of the antitryptic power of the blood, and that a similar change might lead to the breaking down and cure of actinomycotic lesions. With this in view my former colleague, Dr. E. Beaton (1911*) made a number of estimations of the antitryptic power of patients' blood before and after administration of iodide. A slight reduction occurred when the drug was given in doses of from 30 to 60 gr. per diem. A much more striking effect on the antitryptic power was observed when iodine dissolved in potassium iodide was added to serum *in vitro*. One part in 1200 of iodine with 1 in 600 of potassium iodide reduced the antitryptic power by about 65 per cent. when the mixture was incubated for half an hour at 37°C. Half that concentration effected a 20 per cent. reduction. When the same drugs were mixed with trypsin solution in similar concentration its proteolytic power was curtailed to a much smaller degree.

Jobling and Petersen,⁷ working with a similar conception in view, but using a different method for the estimation of the antitryptic power, obtained results which confirmed those of Beaton. The blood of patients to whom potassium iodide was being administered, in doses of 110 gr. per diem on the average, showed a very distinct reduction in antitryptic power. These authors consider the question whether, when iodides are administered to syphilitic and tuberculous patients, iodine is set free in any considerable quantity in the necrotic tissues; and they quote the experiments of O. Loeb,⁸ which suggest that such is the case. Loeb found that unsoftened lymph glands of syphilitic patients contained 3.3 times, and softened glands 6.2 times as much iodine as the blood of the same patients. In conclusion, Jobling and Petersen express the view that “Iodin neutralises the action of the agents which prevent solution and absorption of necrotic tissue, and at the same time lays bare to the action of the real germicidal agent the infecting organism which previously had been protected by the necrotic tissue.” If this view is upheld by further experimental work it might well apply also to the case of actinomycosis and would suggest that good results are to be expected from the administration of iodine in that disease only when necrotic foci require to be broken down. In other circumstances the action of the drug might conceivably be harmful, for *Actinomyces bovis*, like other sero-

* Unpublished researches.

saprophytic microbes, finds a congenial medium in serum whose antitryptic power has been reduced, whereas it is unable to grow in the unaltered serum. It may be noted in this connexion that many observers have reported harmful effects of the use of potassium iodide in tuberculosis.

When we turn to the actual results of treatment by potassium iodide we find very conflicting accounts. In 1898 Poncet and Berard⁹ analysed the records of 105 cases—25 of them severe, 80 of them less severe and considered as favourable to the treatment. These authors recognise the difficulty of apportioning the credit due to the iodide when its administration is only an adjuvant to surgical measures, which manifestly exercise a great effect upon the disease. Their summing up was as follows: "Dans les deux tiers des cas d'actinomycose cervico-faciale ancienne, infectée et ouverte, le résultat du traitement ioduré a semblé nul. Dans les trois quarts des cas d'actinomycose récente, fermée et peu infectée, la guérison a été obtenue par l'adjonction de l'iode au traitement chirurgical, dans un quart par le traitement ioduré seul. Ces derniers résultats ne sont pas sensiblement supérieurs à ceux que l'on a observés après le traitement chirurgical seul ou associé au traitement général. L'iode de potassium ne saurait donc être considéré comme le médicament spécifique de l'actinomycose. . . . Dans les formes viscérales profondes, difficilement accessibles au chirurgien, l'iode n'est susceptible d'entraver l'évolution du parasite que tout à fait à la période de début; mais, à cette période, souvent, le diagnostic reste très hésitant. Plus tard, les infections surajoutées, rendent illusoire l'emploi de l'iode, qui n'agit rarement, à doses massives et prolongées, et encore faut-il, la plupart du temps, qu'une intervention chirurgicale palliative puisse lui venir en aide."

This judgment has been substantially borne out by later experience. It is now generally recognised that the administration of iodide, even in very large doses, has little or no effect upon the more severe infections; while the multiplication of other remedies—e.g., copper salts, methylene blue, X rays, salvarsan, radium, &c.—which have recently been advocated even for the milder infections, shows that the trend of opinion is increasingly unfavourable to the efficacy of the iodide treatment. I would suggest that the latter, if employed at all, should be limited to cases which present large unsoftened foci, and that it should be discontinued as soon as these have broken down.

Speaking generally, the treatment of the patients while under the author's care was (a) by surgical measures, and (b) by the inoculation of vaccines. The surgical measures taken were usually confined to incisions for the evacuation of pus and curetting. In connexion with each of these procedures something was learned from our experience. We learned, in the first place, that a single incision will seldom suffice to maintain satisfactory drainage of an actinomycotic focus. It is characteristic of this infection in man that it spreads by direct extension in contiguous tissues—particularly in the connective tissues—and leads to the formation of small abscess cavities here and there along the line of spread. To check the invasion one must be constantly on the watch for fresh areas of induration and softening, and must resort early to incision of these as often as they appear. My experience leads me to conclude that this policy of early and, if necessary, repeated incisions, is of paramount importance in the treatment of the disease. I think one may go so far as to say that in every focus that is satisfactorily drained the infection by actinomyces will be promptly checked, for this organism, although it can propagate in the fluid of an abscess cavity (which has lost much of its antitryptic power) cannot do so in the unaltered lymph.

This being the case, I would suggest that the principles of treatment advocated by Sir Almroth Wright¹⁰ in connexion with wound infections should be employed here, the incisions being followed up by the intermittent application (every 2–3 hours) of hypertonic salt solution (3–5 per cent.) in order to promote a free flow of lymph through, and out of, the infected tissues. This treatment should be discontinued after a few days in order to facilitate healing.

What we learned in connexion with curetting was that this operation should not be performed with a sharp instrument—which opens up uninfected tissues—but with a dry gauze swab. There is in actinomycosis a fairly sharp line of demarcation between the uninfected and the infected tissues, and since the latter, in process of erosion, are very friable, it is usually possible to remove them almost in toto on a

swab, leaving the wound with so little infection that it can easily be dealt with by the leucocytes. In one of the later cases of the series here reported an abscess nearly as large as a closed fist was treated in this way after incision and forthwith sewn up. It healed by first intention in a week.

I would therefore emphasise two points in connexion with the surgery of the disease: first, the necessity of maintaining efficient drainage throughout the course of the illness; and secondly, dry curetting by means of a gauze swab. The question, of course, arises as to how far these measures are applicable to abdominal and thoracic cases, when, as is frequently the case, the diagnosis has been made only after the infection has extended considerably beyond the original focus. It seems to the writer that, by the aid of stereoscopic skiagrams taken after the injection under pressure of a bismuth suspension, one might be able in such cases to trace the chief ramifications of the infective process, and thereafter proceed to deal with each of these by curetting and "salt suction" as above described. An extensive operation of this kind would seem to be justifiable in view of the very high mortality attaching to these cases.

TREATMENT BY VACCINES.

Several considerations led us to hope for success in the treatment of these infections by active immunisation. In the first place, actinomycosis is a disease which progresses but slowly, and does not, as a rule, seriously injure the patient's general health for a considerable period; there is, therefore, if the diagnosis is made fairly early, abundant opportunity for a satisfactory response to the inoculations of vaccine. Again, the disease shows a tendency to spontaneous cure, given a satisfactory outflow for collections of pus. This circumstance presumably stands in relation to the fact that the organism is unable to grow in the unaltered blood fluids and is readily ingested by the leucocytes. It is probable, therefore, that even a small response to the inoculation of vaccines would suffice to turn the scale against the progress of the infection.

Up to the present the writer has treated some 23 cases by this method, always in association with simple surgical measures, as outlined above. In all cases a vaccine prepared from strains of *Actinomyces bovis* of human origin was employed, and most of them received in addition other vaccines corresponding to their respective secondary infections. Autogenous actinomyces vaccines were used for 11 cases, most of the remainder being treated by the polyvalent stock vaccine prepared at St. Mary's Hospital and issued by Messrs. Parke, Davis and Co. Standardisation of the vaccines was carried out by making approximate counts of their mycelial fragments after the growths had been broken up by forcible shaking. Since this breaking up, however, is at best very imperfect, there is much to be said in favour of abandoning the method of enumeration by counting and replacing it by the procedure employed for the issue of tuberculin (bacillary emulsion)—viz., grinding an ascertained weight of dried culture. The writer has adopted this latter practice since the war. A considerable growth of the organism was obtained by inoculating a pure culture into one or more Erlenmeyer flasks of glucose broth under oil; when fully grown the supernatant fluid of these flasks was decanted, the deposit of actinomyces was collected, washed, and then dried over sulphuric acid in vacuo, the dry flakes being finally ground in a Hayden mortar and emulsified in saline. That actinomyces vaccines so prepared are capable of acting as satisfactory antigens was demonstrated by the inoculation of rabbits, which responded in every case by a development of agglutinins.

Some Particulars with Regard to the Treatment by Vaccines.

An attempt was first made to control the dosage of actinomyces vaccine by measurements of the patient's opsonic power, using for this purpose a strain of the organism which had acquired a largely bacillary habit of growth on artificial media. The phagocytic preparations so obtained were not all that could be desired,

but they afforded a rough indication that the appropriate dose was about 5-10 millions of mycelial fragments. Proceeding on this basis we have generally commenced the treatment with doses of 2 or 2½ million fragments at intervals of five days, and gradually increased the quantity as guided by the progress of the patient. The best results have usually been obtained with doses of from 4-10 million fragments. In a few cases which were not improving on smaller doses the quantity has been considerably increased—in one case to 75 million fragments—but without any apparent advantage.

Reaction.—In several instances the inoculation of vaccine was followed by a rise of temperature, but this did not occur with regularity in any patient. As a rule there was no constitutional disturbance of any kind, the actinomycotic focus showed no increased congestion, and at the site of inoculation there was no appreciable reaction.

Treatment of the associated infections by the appropriate vaccines.—In an earlier report on "The Mycelial and other Micro-organisms Associated with Actinomycosis"¹ the writer has called attention to a small cocco-bacillary microbe which is frequently to be found in great numbers along with actinomyces in the actinomycotic granule. This microbe has been described previously by Klinger¹¹ under the name *Bacterium actinomycetum comitans*. The significance of its association with the mycelial organism in actinomycosis is far from clear at present (the question is discussed at some length in the paper referred to), but it was hoped that something might be gained by combining inoculations of a vaccine of this bacterium with that of actinomyces. Twelve of the patients were so inoculated, the doses of vaccine varying from 5 to 400 millions of the bacterium. As in the case of actinomyces vaccine, the inoculations of this bacterium did not as a rule give rise to any appreciable reactions. The more common secondary infections, such as those by staphylococci, streptococci, diphtheroid and coliform bacilli, were also combated by the appropriate vaccines.

The Results of Vaccine Treatment.

The inoculated cases comprise: 11 cervico-facial infections, with which may be included 1 of the hand; 6 thoracic infections; 6 abdominal infections. The first group—of 11 cases—included two which were decidedly unfavourable to any treatment. One of these was a girl who had symptoms of intracranial pressure before admission to hospital (ten months from the onset of the disease), and died in a short time with a large temporo-sphenoidal abscess. The second was that of the man previously mentioned, in whom the disease had involved a large part of the mandible. Mr. Cope performed an extensive resection from which the patient made an apparently complete recovery and was able to join the army. Recently, however, the disease recurred in a very small focus in front of the ear, but the patient is again under vaccine treatment and the infection is making no headway.

The remaining nine cases of this group were of lesser degrees of severity, but in most of them the infection had been in progress for several months before they came under treatment. All recovered, and have not, so far as I have been able to ascertain, had any recurrence during the 4-6 years that have elapsed. In the least extensive cases a period of 3-6 weeks sufficed for cure, but in others a much longer time was required and many inoculations. Whenever bone was involved the recovery was very slow.

Of the six thoracic cases none have been saved. In considering this melancholy failure it should be made clear that in all of them the disease had made considerable headway before vaccine treatment was instituted. In one case 10 months had intervened since the symptoms were first noticed, and in the other cases 8, 7, 5, 3, and 3 months respectively. One case was particularly disappointing, but his record is not without grounds for hope.

The patient, a school teacher of 43, was sent to Sir Almroth Wright by Sir John Collie. Two months previously he had been operated on by Mr. J. Sherren at the London Hospital for an extraperitoneal abscess in the left iliac fossa and

another abscess over the left shoulder. In spite of treatment by potassium iodide, further lesions had developed on the back of the neck, the shoulder, and the left costal margin, and the man was very ill on admission to St. Mary's. The lesion on the costal margin suggested the probable existence of a pulmonary focus, but definite evidence of this was not obtained at that time. From the first inoculation of vaccine he began to improve rapidly, his fever subsided, and several of the lesions healed. After four months he was permitted to resume his work, which he carried on for some three years, although one or two small lesions were never quite dried up. Sir John Collie¹² wrote enthusiastically of the progress he had made. Unhappily the cure was not so complete as we hoped at that time. Although he was an excellent patient and continued faithfully with the inoculations over a very long period, the pulmonary lesion reasserted itself four and a half years after the onset and he went down hill. Judging from the clinical course of the other thoracic cases, and taking into account his serious condition when he came under treatment, it seems legitimate to suppose that without vaccines this man would have succumbed within 18 months from the commencement of the disease—probably within a year. Why we were able to achieve so much in his case, and finally failed, is not clear. In part it may have been due, as he himself thought, to his becoming very depressed over personal war anxieties.

With regard to the six abdominal cases much the same considerations apply. The five of them who died had been ill for 13, 8, 6, 5, and 5 months respectively before they were transferred to us for treatment. Three of them had already the cachexia and the particularly offensive discharge which are so often associated with this condition when it attacks the abdomen, and which are presumably due to a very severe secondary infection. (So far we have not been able to determine which particular microbe or microbes are responsible for the smell.) In these five cases one cannot say that anything was achieved by treatment. The sixth case was less severe than the others. The infection had been recognised about eight weeks after the original operation by Mr. Cope for appendicular abscess, and although there was irregular fever—sometimes to 102° F.—the cachexia and the offensive discharge never developed. Thanks to a small perforation of the ileum which developed early in the course of the disease we were enabled in this case to secure favourable drainage by means of a counter opening in the buttock. It is difficult to decide how much of the credit for her recovery should be allotted to vaccine treatment, and how much to this efficient drainage. Probably each factor was of importance. (This patient's recovery suggests that it might prove worth while in similar circumstances to secure favourable drainage by trephining the ileum from behind.)

CONCLUSIONS WITH REGARD TO VACCINE TREATMENT.

The opinion I have formed from my experience up to date is as follows: the treatment of actinomycosis by vaccines facilitates recovery when efficient surgical drainage of the affected tissues is secured and maintained; when, however, drainage is unsatisfactory the use of appropriate vaccines will not usually suffice to stay the progress of the infection. In support of the first part of this opinion I am unable to offer any evidence which will carry conviction on paper—it is manifestly difficult when dealing with a condition like cervico-facial actinomycosis, which tends to recover spontaneously if drained, to be certain that cure has been hastened by any indirect therapeutic measures. In three or four of my cases, however, which had hung fire for several weeks or months, improvement took place so promptly and so rapidly after the commencement of inoculations that there seemed to be no doubt as to the efficacy of the treatment, and this opinion found further support from the case of thoracic infection whose story has been told above.

With reference to the failure of vaccine treatment in cases whose lesions are not satisfactorily drained I would suggest that this may be due in a large part to the blood stream having very little access to those lesions by reason of the zone of "wooden" induration which habitually surrounds them.

It will be noticed that my failure to secure good results in most of the thoracic cases contrasts unfavourably with the striking cure reported by Dr. Wynn (1908).¹³ Fortunately, Dr. Wynn described in some detail the characters of the streptothrix infecting his case, and on examining his record it becomes clear that he had to deal with quite a different infection from that with which the present writer is here concerned. That being the case, we cannot properly contrast the results of vaccine treatment in the two infections.

The points on which is based the opinion that Dr. Wynn's streptothrix was not *Actinomyces bovis* (Wolff-Israel) are the following:—

(1) The record says: "The pus or sputum, when stained by Gram's method, showed enormous numbers of delicate, thread-like filaments of fairly uniform thickness." In infections by *Actinomyces bovis*, such as the writer's cases, it has been quite exceptional to find mycelial elements free in the pus; they are almost entirely confined to the granules, and, unless one of these is consciously crushed, the threads will not become disseminated in preparing a film of pus or sputum. Occasionally, of course, one may chance to find a microscopic cluster of threads, presumably an embryo "granule."

(2) "Numerous spores were seen, but no clubs." In none of the writer's cases were spores seen, nor in the 13 cases reported by Homer Wright.¹⁴ Clubs were found whenever they were looked for—i.e., in rather more than 75 per cent. of my cases.

(3) In describing its cultural characters Dr. Wynn says of his organism: "It grows readily on ordinary media at 37° C., much less readily at room temperature. It grows under both aerobic and anaerobic conditions, but more freely under the former." Here are three points in which the organism contrasts with *Actinomyces bovis*. The latter does not grow readily on ordinary media; does not grow at all at room temperature; and, although it will occasionally give a very sparse growth under aerobic conditions it is decidedly an anaerobic organism.

(4) Again, Dr. Wynn found that at 37° C. growth appeared after 24 hours on agar. Cultures of *Actinomyces bovis* very seldom appear before three days on agar—more commonly not until 4-6 days.

With regard to gelatin stabs, Dr. Wynn's record says, "Growth slower, but after four days discoid colonies form." *Actinomyces bovis* will not grow at all in solid gelatin.

The three or four cases I have seen of infection by streptothrices other than *Actinomyces bovis* have been of decidedly milder clinical type than those of thoracic and abdominal actinomycosis.

SHOULD AN AUTOGENOUS OR A POLYVALENT STOCK VACCINE OF ACTINOMYCES BE EMPLOYED?

The answer to this question turns chiefly on considerations of the degree of difference found to exist between individual strains of *Actinomyces bovis*. The 21 strains isolated in pure culture by the author have shown a close conformity in respect of their cultural characters, viability, and staining reactions. Their morphology has not been minutely studied, but no gross differences have been observed—apart from a somewhat unequal tendency to assume a bacillary habit of growth in subcultures. On the other hand, it has been suggested by the result of some few agglutination tests that the species *Actinomyces bovis* comprises more than one serological type. The following is a record of one such agglutination test:—

Three rabbits were inoculated with typical strains of *Actinomyces bovis*—viz., "G 1," "G 4," and "Arthur" respectively. When their sera were tested against emulsions of the three strains the agglutination observed was as shown in Table II. (A, B, C).

In view of these findings—the agreement in respect of general cultural characters and the divergence in regard to serological type—it would seem probable that a stock vaccine would serve as well as an autogenous one if, at any rate, it included representatives of the different types. But this latter condition is not easy of realisation at present, for the determination of types can only be slowly accomplished as a considerable number of strains accumulate for study. For the time being, therefore, I think that an autogenous vaccine should be employed whenever practicable, but, since a

period of three to four weeks will often be necessary for its preparation, treatment should always be commenced with a polyvalent stock vaccine.

TABLE II.—(A) Rabbit Inoculated with Emulsion of Strain "G 1."

Serum.	Dilutions of serum.				
	1:50	1:100	1:200	1:400	1:800
Strain "G 1" ...	+++	+++	++	+	Trace.
" " "Arthur" ...	+	+	0	0	...
" " "G 4" ...	++++	++++	+++	++	...

(B) Rabbit Inoculated with Emulsion of Strain "Arthur."

Strain "Arthur" ...	++++	+	0	0	0
" " "G 1" ...	+++	++	0	0	0
" " "G 4" ...	++++	+++	++	Trace.	...

(C) Rabbit Inoculated with Emulsion of Strain "G 4."

Strain "G 4" ...	++++	++++	+++	+++	++
" " "G 1" ...	Trace.	0	0	...	...
" " "Arthur" ...	0	0	0	0	...

+++ , ++ , + = Incomplete agglutination, of varying degrees.
++++ = Complete agglutination. 0 = No agglutination.

DISCUSSION.

(1) CONCERNING THE TERM ACTINOMYCOSIS.

There is, unfortunately, a great deal of confusion with regard to the use of this term. In what follows I shall try to show that under it have been included in the past at least four classes of cases. As a consequence our knowledge of these infections has become less, rather than more exact, and progress in the direction of better treatment has been undoubtedly handicapped. The recent application of vaccine therapy to these cases makes it particularly desirable that we should deal, as far as possible, with homogeneous groups of cases, and give to these groups distinguishing names. Lignières and Spitz,¹⁵ recognising the need for a more precise nomenclature, have suggested that it would be well to abandon altogether the old term and substitute for it "actinophytose," adding specific subtitles for the several classes of cases. There is something to be said for this proposal, but more, I think, in favour of retaining the older term, to be used in a definitely restricted sense, and of introducing one or two new terms for the infections which are separated off by those restrictions. We may now consider what restrictions it might be well to put upon the term actinomycosis.

The origin of this term dates back to the discovery of the well-known radiating arrangement of "clubs" round the "sulphur granules" derived from certain granulomatous lesions of cattle and of man. So far as was known at that time such granules were always composed of a feltwork of branching mycelium. It is readily understood, then, that the presence of "granules" came to be regarded as diagnostic and pathognomonic of actinomycosis. When, with the introduction of artificial media, cultures were obtained from some of these infections, several quite distinct organisms were reported by different investigators, the types which attracted most attention being (1) an easily grown, aerobic variety, described by Boström¹⁶ and others; and (2) an anaerobic variety, grown with difficulty, described by Wolff and Israel.¹⁷ In view of these discordant results of the earlier bacteriological work it came to be believed that there was no one infective agent responsible for actinomycosis, but that several more or less allied micro-organisms could produce the disease.

The work of the past 20 years, however, has brought to light two facts which require us to recast the earlier views. It has shown (1) that the production of granules with clubs is not pathognomonic of actinomycosis; the same thing occurs in various conditions which are not mycoses at all but bacillary infections, and sometimes is associated with clinical conditions totally different from those of actinomycosis. (2) That of all the human infections which are productive of "granules" and show

the well-known clinical features of actinomycosis, the great majority are due to one and the same mycelial species—viz., that described by Wolff and Israel.¹⁷

It will be conducive to clearness if we consider these two statements separately. Beginning with the first, the evidence that granules are formed in conditions other than actinomycosis is as follows: Lignières and Spitz¹⁸ have described an infection of cattle which gives rise to granulomatous tissue not unlike those of actinomycosis, but in which the “sulphur granules” (showing typical clubs) are composed entirely of Gram-negative bacilli. They gave the name “actinobacillose” to this condition and that of “actinobacille” to the microbe. These authors state that this infection is widely spread in the world. Nocard¹⁹ reported cases in France in 1902, and in 1915 Griffith²⁰ examining so-called actinomycotic material (chiefly tongues) derived from cattle killed in England, made the important discovery that no less than 40 out of 44 specimens presented lesions which were apparently due to this bacillus and not to a mycotic infection. So far as I am aware, only one human case has been reported (Ravaut and Pinoy,¹² 1911).

Apart from actinobacillosis it is well known that the injection of tubercle bacilli will, in certain circumstances, give rise to club formation around the masses of bacilli. Further, Lignières and Spitz¹⁵ state that granules with clubs (“massues rayonnées”) may occur in animal infections produced by various other microbes—e.g., by the butter bacillus of Rabinowitsch, the bacillus of Cozzolino, the hay bacillus of Möller, &c. Quite recently a very interesting human infection associated with the production of granules has come to my notice through the kindness of Miss Aldrich Blake and Dr. Lepper, by whose permission I am enabled to refer to it. A young woman was admitted to the Elizabeth Garrett Anderson Hospital with a tumour in the left loin which proved to be an abscess connected with a tuberculous kidney. The pus evacuated from this abscess showed a large number of granules, similar in size and naked-eye appearance to those of actinomycosis. Under the microscope, however, no clubs could be seen nor any mycelium—the granules were composed of masses of Gram-negative bacilli, 2.5–5μ in length and about 0.6μ in thickness. An organism corresponding to these bacilli was cultivated aerobically on agar, growth occurring in 24–48 hours in the form of flat, semi-transparent colonies of about 1½ millimetres diameter. It is a facultative anaerobe, does not grow at room temperature, and has not been observed to form spores. It is actively motile, and is not acid-fast. I have been unable to identify this organism, which seems to be quite distinct from the actinobacille of Lignières and Spitz.

From the fact that this bacillus had disappeared from the pus within a week of the first drainage operation I conclude that it was probably a saprophytic invader of the abscess cavity.

We may pass now to the statement that the great majority of actinomycotic infections are due to one microbic species—viz., the anaerobic type *Actinomyces bovis*† described by Wolff and Israel.¹⁷ The data relating to that conclusion may conveniently be set out in the form of a table (Table III.) showing the more important of the records of bacteriological investigations made during the past 20 years.

It will be seen from Table III. that in seven different parts of the world one and the same type of mycelial organism—viz., that described by Wolff and Israel (1891)¹⁷—has played a predominant part in the actinomycotic infections both of man and cattle. (That this was not recognised from the first is, no doubt, largely due to the circumstance that methods of anaerobic cultivation were but little developed and applied when the earliest observations were made.) From a very small minority of cases quite different organisms were cultivated. In two instances at least these were aerobic species, and it seems not improbable that they were present merely as air-borne contaminations. Whether that was the case or not, it is important to note that isolated instances are on record in which it seems clear that an aerobic mycelial organism productive of typical

granules in vivo has given rise to suppurative lesions—e.g., Wynn’s case referred to above and that of de Nooy⁷ recently reported from Java.

It should be particularly noted that the bacteriological findings summarised have reference only to infections which yielded typical “granules” in the discharges. The results would have shown much less

TABLE III.

(A) Number of cases from which cultures were obtained and the type of mycelial organism determined.

(B) Number of cases from which *Actinomyces bovis* (Wolff-Israel) was cultivated. It is not claimed that the description given by each investigator for the strains included in this column tallies exactly with that of Wolff and Israel. There is, unfortunately, at present no touchstone by which to decide unequivocally whether a given strain is or is not identical with the type Wolff-Israel. The figures given should, therefore, be taken to mean that each investigator himself regarded so many of his strains as showing a general correspondence with that type.

(C) Number of cases from which an anaerobic mycelial organism quite distinct from *Actinomyces bovis* was cultivated.

(D) Number of cases from which an aerobic mycelial organism was cultivated.

Name of investigator, date of publication, and country in which the cases occurred.	Infections of man.				Infections of cattle.			
	(A)	(B)	(C)	(D)	(A)	(B)	(C)	(D)
Levy ²² (1899), Germany	5	5	0	0	—	—	—	—
Schukevitch ²³ (1903), Russia	—	—	—	—	25	22	—	3
Homer Wright ¹⁴ (1905), U.S.A.	13	13	0	0	2	2	0	0
Shiota ²⁴ (1909), Japan	29	28 (a)	—	—	—	—	—	—
Harbitz and Grondahl ²⁵ (1911), { Norway	20	20	0	0	—	—	—	—
Pinoy ²⁶ (1913), France	3	2 (b)	—	—	16	14	—	2
Colebrook ¹ (1920), England	24	21	2 (c)	1 (d)	—	—	—	—
Totals	94	89	2	1	43	38	0	5

- (a) The character of the one remaining strain not described.
(b) One strain not identified.
(c) It is doubtful whether these two strains were really distinct from *Actinomyces bovis* or merely variants of that type. They showed slight differences in respect of their cultural characters, but owing to pressure of other work were not fully investigated.
(d) A single colony of the mycelial organism was cultivated from this case.

uniformity had the several investigations included in their purview all those cases in which Gram-staining mycelium—irrespective of its aggregation into naked-eye granules—was present in the discharges.

With this summary of new knowledge in mind we may come back to deal with the problem of nomenclature. There appear to be four classes of cases which it is desirable to define and to distinguish by different names. They are:—

(a) Cases which show granules composed of Gram-staining mycelium, and from which a micro-organism of the type *Actinomyces bovis* (Wolff-Israel) is isolated by culture. To this class, which will be by far the largest of all the granule infections—in man, at any rate—I should restrict the term actinomycosis.

(b) Cases which show granules composed of Gram-staining mycelium, but this mycelial organism proves on cultivation to be distinct from the type *Actinomyces bovis* (Wolff-Israel). For this class, which I think to be a small one, I would propose the term “Paractinomycosis.” The cases reported by Wynn¹³ and de Nooy²⁶ were of this kind.

(c) Cases which show granules composed, not of mycelium, but of bacillary organisms. For these the term Actinobacillosis, proposed by Lignières and Spitz, might well be retained, adding, whenever possible, a specific subtitle to denote the particular bacillus in question.

(d) Cases which show an infection by a Gram-staining mycelial organism, but the mycelium is not aggregated into granules visible to the naked eye. To this class, which I take to be a heterogeneous, and not a very small, one, a name with the prefix “actino” would seem to be inappropriate. The term streptothricosis, which has frequently been employed to designate these cases in the past, might well be retained, and a specific subtitle appended to it whenever the particular infecting agent can be identified with a recognised type of organism.

When, as will often happen, attempts to cultivate the mycelium from a case with typical granules are either not made or are not successful it would seem justifiable—in view of the findings shown in Table III.

† In adopting the name *Actinomyces bovis* for this type I follow the usage which seems to have the most general support. Some writers, including Lignières and Spitz, have held that the name properly belongs to the quite different aerobic organism described by Boström and others.

—to label the case provisionally as one of actinomycosis. For the purposes of scientific records, on the other hand, the isolation of the organism is, in my opinion, essential.

(2) WHAT IS THE SOURCE OF INFECTION IN ACTINOMYCOSIS?

The answer to this question is given—either definitely stated or implied—in every surgical and veterinary textbook. But is it true? The “ray fungus,” we are told, has its habitat in soil, on grain, straws, and other vegetable matter and is conveyed by these to the tissues of man and animals. This belief is chiefly due to the advocacy of Boström,¹⁶ who, in 1891, published a report of a laborious investigation on the subject. He observed that cattle grazing in marshy districts frequently developed actinomycosis, and that moulds were met with on the vegetation of such districts, which showed some resemblance to certain mycelial organisms which had occasionally been cultivated from actinomycotic discharges. (For criticism of this latter part of the work see Homer Wright’s paper.¹⁴) Further, on examining the mouths of cattle Boström noticed that particles of vegetable matter were very frequently forced down between the teeth and gums, and he concluded that these particles probably carried the infection into the tissues. By means of serial sections he succeeded in demonstrating minute fragments of vegetable matter (barley “whiskers”) in several instances, and he reports in detail the case of a woman who developed a submaxillary abscess, in the pus of which a similar tiny particle of barley (1×0.2 mm.) was detected.

This chain of evidence is not, however, very satisfactory when looked at from the standpoint of to-day. We now know, as has been shown above, that an anaerobic species (*Actinomyces bovis*), and not the organism described by Boström, is most commonly the infecting agent in actinomycosis, of man at any rate. Secondly, *Actinomyces bovis* has never, so far as I am able to ascertain, been met with outside the animal body. There are many species of actinomycetes recoverable from soil, but all appear to be aerobic organisms with characters quite different from those of *Actinomyces bovis*. Harbitz²⁵ reports an attempt of Hagen to recover the latter organism from “natural” sources in a part of Norway where actinomycosis was fairly common. He investigated 9 strains of mycelial organisms (3 obtained from the air, 2 from straw, 3 from barley and oats, and 1 from manure), but all were compulsory aerobes. Thirdly, *Actinomyces bovis* is a very delicate organism, which grows only at temperatures near that of the human body and very sparsely, if at all, in the presence of air; it also dies out very readily, especially when dried, and has not been shown to form spores. Having these characters, there is little likelihood that it has its “natural” habitat outside the human and animal body. Again, it is, perhaps, significant that the incidence of actinomycosis seems to be no greater among the agricultural population than among town-dwellers; and women are affected almost as frequently as men. Finally, it may be remarked that only in a very small percentage of cases is there any record of a vegetable foreign body having been evacuated from the primary abscess or a history which suggests the probability of this mode of infection. Only one of the author’s 25 cases had such a history.

In view of all the above considerations it seems highly improbable that infection is usually conveyed to man in the manner suggested by Boström. At the same time one must acknowledge that there are a fair number of well-attested cases on record in which infection seems definitely to have followed the impaction of vegetable material. To cite only two—there is the case reported by Soltman (quoted by Poncet and Berard,⁹ p. 42) of a boy who swallowed a head of barley which apparently stuck in his oesophagus and later worked its way out through an abscess in the sixth intercostal space, and another instance which occurred in my own experience of a piece of grass being evacuated from the submaxillary abscess of a boy. The grass was said to have “stuck in his throat” about a month previously.

(It may be noted that the one case described at length by Boström in support of his thesis was apparently not a genuine actinomycosis, for he expressly mentions that there were no granules or clubs, and the mycelium was distributed freely in the pus.)

With regard to cases of this kind, two considerations suggest themselves. Firstly, it may happen that an infection is sometimes introduced into the tissues on grain, straws, &c., but that the infecting organism so introduced is something other than *Actinomyces bovis*. This was probably so in Boström’s case just referred to. In the second place, Homer Wright has pointed out that the development of actinomycosis following the impaction of a piece of straw, grain, &c., in the mucous membrane does not necessarily imply that the infecting organism was conveyed on that foreign body. It is conceivable that the impaction merely favoured infection by an organism which was pre-existing as a saprophyte in the mouth or other part of the alimentary tract. That actinomyces may at times be present in the mouth of a normal individual was strongly suggested by the history of a case which Mr. Cope has reported (vide Case 13 of his series).² This patient injured the knuckles of his hand by contact with an opponent’s teeth. An acute cellulitis ensued, and was followed by the development of a typical, indolent, actinomycotic lesion, which persisted for three months before he came to the hospital. A similar case has been reported by McWilliams²⁸ in America. Further evidence has been furnished by Lord.²⁹ Having observed fragments of Gram-staining mycelium resembling actinomyces in the contents of carious teeth and tonsillar crypts (of patients free from actinomycosis) he made an emulsion of these and inoculated it into laboratory animals. Small lesions were produced which showed on section the formation of actinomycotic granules. Unfortunately he did not complete the investigation by the isolation of actinomyces from these lesions. Further observations of this kind should go far towards resolving the problem.

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PLAGUE IN SOUTH AFRICA.—Several deaths of natives from plague have occurred in the Orange Free State during March. Bacteriological examinations have confirmed the diagnosis. The infection exists amongst, and is being perpetuated and spread by, wild rodents, and possibly also, it is stated, by small carnivora, such as the muishond and meerkat, the flea being the connecting link with man in the chain of infection.