patients with no venous pulse the effect of digitalis in depressing conductivity can be recognized by the finger or by a tracing of the radial. I think I can assert with confidence that in any given case, when the auricles are active, when, in response to the administration of digitalis, the pulse becomes irregular, with long pauses, these pauses are due to the propping out of ventricular systoles, because the stimulus has failed to pass from auricle to ventricle. To my mind, the only other cause which could occasion these long pauses is the occurrence of extra systoles, but on listening over the heart the sounds of the heart are absent when a ventricular systole drops out; whereas, with extra systoles, the characteristic short, rapid sounds can be heard, due to the premature contraction of the ventricles.

I quote the following case to show how the nature of the arrhythmia can be proved with fair probability without the presence of a venous pulse to guide us:

Female, aged 53. She has suffered from attacks of palpitation, for which I have attended her at intervals for many years. She consulted me in April, 1904, for great shortness of breath and violent throbbing in the neck and upper part of the chest. The pulse was usually from 90 to 100 beats per minute, full and forcible. There was marked pulsation in the carotid, but no venous pulse. There was a faint apex beat in the fifth interspace, and the heart's dullness extended to the left 1 in. beyond the nipple. There was a rough systolic murmur at the apex, also well heard at the base. I was doubtful whether there was not also a slight aortic systolic murmur. There were no murmurs during my previous attendances on this patient. Notwithstanding rest and appropriate treatment she did not improve, and in June she visited Nauheim, and there underwent a six weeks' course of treatment—baths and exercises—followed by a visit to Switzerland. She returned to Burnley distinctly worse, very much thinner, less able to undertake exertion because of the palpitation and breathlessness, and the pulse rarely under 100 beats per minute. I tried her with various remedies, including digitalis; but in a few days this drug produced such gastric derangement that I had to stop it. She steadily got worse, and, as there was sleeplessness and much muscular tremor I prescribed ammonium bromide. In a few days she had an extensive attack of erythema nodosum on both legs. She recovered from this in a fortnight, being kept in bed and gently massaged. I resolved again to try the effect of digitalis. She began with three granules of digitalin a day on September 18th. No effect was observed till September 20th, when her heart began to intermit very frequently, sometimes she said she could feel it miss every second beat for hours. When I examined her on September 26th the pulse-rate varied in its rhythm, periods of perfect regularity varying with periods of irregularity as in Figs. 7 and 8.

Fig. 7.—Tracing of the radial pulse, showing irregularity due to digitalis. The nature of this irregularity is shown in Fig. 9. The minute elevation preceding the fall at x is due to the systole of the left auricle.

Fig. 8.—Shows the same as Fig. 7. The nature of this irregularity is shown in Fig. 10.

During the intermissions no sounds could be detected in the heart. The digitalis was stopped, and the arrhythmia daily got less until the 4th of October when it had entirely disappeared. Since that date the pulse has never shown a single irregularity, the heart has become much quieter, the rate gradually falling as low as 72 beats per minute. The heart's dullness is now within the nipple line, the murmurs are still present, but the patient's general health has wonderfully improved. Although the improvement dates from the period of arrhythmia, the patient has a horror of the digitalis.

While the absence of a venous pulse deprives us of the absolute proof of the nature of the arrhythmia we can infer that depression of conductivity was the cause from the similarity of the irregularity to that shown in Figs. 2 and 3. The nature of this arrhythmia becomes all the more evident if we construct diagrams on the basis of the two tracings Figs. 7 and 8.

Fig. 9.—Diagram constructed to show the action of the heart when Fig. 7 was taken. For explanation see Fig. 4.

Fig. 10.—Diagram to show the action of the heart when Fig. 8 was taken. For explanation, see Fig. 4.

Fig. 10 is a diagram representing Fig. 8, and shows the nature of the arrhythmia in this instance. In constructing these diagrams, I have represented the auricular systole as appearing with mathematical regularity. As a matter of fact, however, there is usually a slight variation in the rhythm of the auricular systole, and a slight delay in its occurrence might slightly modify the time represented as having been spent by the stimulus crossing the A-V fibres. Further facts connected with this form of arrhythmia will be found in Wenckebach's book. This author had predicted that if digitalis were employed in a case of irregular pulse due to depressed conductivity, it might depress the conductivity to a dangerous extent.

On March 7th, 1905, this patient developed again this arrhythmia and at the same time a venous pulse appeared in the neck. I have taken numerous tracings of the jugular pulse and on analysis find that the above interpretation is verified in every particular.

The Milroy Lectures

ON

INDUSTRIAL ANTHRAX.

Delivered before the Royal College of Physicians of London.

By T. M. LEGGE, M.D. OXON.,

H.M. Medical Inspector of Factories.

LECTURE II.

[ABSTRACT.]

TREATMENT OF EXTERNAL ANTHRAX.

THE treatment of anthrax until recently has either been merely expectant or consisted in cauterization or other allied treatment of the local pustule. But the use of a serum derived from an immunized animal is coming more and more into use, especially in Italy and South America. Since in external anthrax spontaneous cures are frequent, a consideration of mere case-mortality will not suffice to establish the relative value of the three methods of treatment mentioned. Other points must be considered, such as (1) the relative amount of scarring or of deformity left; (2) the applicability of the form of treatment to the different types assumed by the disease and the stage which it may have reached; and (3) the length of time which elapses from the beginning of the treatment to resumption of employment. The third point is of especial moment in connexion with an industrial disease.

Muller¹ has described 13 consecutive cases treated successfully in Jena by rest, fixation, and elevation of the part affected, stimulating diet, and the local application of grey ointment. Ramstedt² from the same clinic, has adduced more recently other 7 consecutive cases (one very severe), in which nothing but the same expectant treatment was pursued. And, similarly, Fr. Schultze³ of Bonn has cited a case of extremely severe malignant pustule of the cheek, with extensive oedema of the eyelid, neck, and chest, which was cured after a plastic operation on the eyelid without other operative treatment. Muller, too, considers that the adoption of expectant treatment may be defended on the ground that any operation may facilitate the distribution of the bacilli throughout the system.

Surgical interference usually takes the form of free excision, dissecting out the pustule from the healthy tissues beneath, swabbing the wound out with pure carbolic, and allowing the wound to granulate up from the bottom. Subcutaneous injections of 5 per cent. carbolic acid around the malignant

pustule have also been employed. At Guy's Hospital, again, Davies Colley,⁴ basing his practice on that of Muskett in South Africa, has, in addition to excision, powdered ipecacuanha on the wound, and given it in 10 gr. doses internally. Muskett⁵ in 15 years thus treated 50 cases without fatal issue, using locally ipecacuanha mixed with water into a cream, and did not practise excision. He believed the remedy was a specific. Washbourn found that the powder had the power of destroying anthrax bacilli, but not the spores; in the body sporulation does not take place. This treatment is still most frequently employed at Guy's Hospital. In Russia⁶ treatment by injections of carbolic acid has been largely used. Scharnowski has treated in this manner 50 cases, with 2 per cent. of deaths; their severity may be judged from the fact that in 25 the face and neck were affected.

Cauterisation with caustic potash has also been in favour, and Graef⁷ has reported 384 cases thus treated by himself and two others, with a mortality of 5 per cent.

It has been already stated that the general mortality to be expected in anthrax is 25 per cent., but for cases treated early and under favourable conditions this is too high. Even, however, in districts where the disease is well known patients commonly defer applying for treatment much too long. Early excision—not later than the fourth day—is good; later on it seems possible to believe that it may promote generalization of the disease. In some situations, moreover, in which anthrax occurs excision is either impracticable or will necessitate subsequent and serious plastic operations and prolonged treatment.

SERUM TREATMENT.

Turning now to treatment by antianthrax serum, I have examined the details of all the published cases that I can find*—67 in number. All but 2 of the cases have been treated in Italy with Sclavo's serum.

Of these, 56 were treated by serum alone, and in 11 this serum treatment was subsequent to other treatment, which in 10 cases had been excision or cauterization, or both. In 44 of the 56 treated with serum alone the data given are precise enough to determine the time which elapsed between the commencement of treatment and complete recovery. In several instances it is the same as the time given for the separation of the eschar, but many days before that stage the patient was to all intents and purposes quite well, excluding the fatal cases. In every instance but one by the third day marked improvement had taken place, not only in the general symptoms but in arrest of the further development of the pustule and in diminution of the oedema. Taking the time thus given or to be inferred in these 44 cases, the average duration of treatment was eight days. In none was it more than fourteen days. I can affirm, too, that in the 12 cases treated with serum alone in which the details are not precise enough to allow of the number of days being given, the evidence all points to rapid healing except in 2, where there was loss of tissue. The exact description, so far as it is given of the final condition at the site of the pustule itself, is as follows:

No visible scar	...	...	...	10
Scar hardly visible	...	...	...	5
Slight scar	...	...	...	10
Completely cured	...	...	...	15
Some loss of tissue in eyelid but function unimpaired	...	...	...	1
Complete loss of upper eyelid	...	...	...	1

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The site of the lesion was on the neck, 15; cheek, 13; eyelids and eyebrow, 9; other parts of the face, 13; and arm and hand, 12.

As for the 2 fatal cases: In the first the patient was the subject of malaria, was addicted to alcohol, and had syphilis. The pustule was on the upper eyelid, with oedema extending rapidly over the face and chest, and there was no necrotic patch to assist in the diagnosis. The condition was suspected to be diphtheria of the conjunctival mucous membrane, and diphtheria antitoxin was injected. A day later some vesicles appeared on the eyebrow, and then 40 c.cm. of antianthrax serum were administered. After this he improved rapidly and materially for four days, but then had a rigor, followed by collapse and death. *Post mortem*, extensive submeningeal effusion containing anthrax bacilli was found.

In the other case, also affecting the eyelid, serum treatment

was delayed, owing to the impossibility of obtaining it, so excision was practised. When the serum was obtained and injected endovenously, immediate improvement took place. Two days later the oedema had diminished so much that the woman was able to see out of her eye, took her food well, and the pulse-rate dropped from 140 to 104. A few hours later she was seized with sudden collapse, cyanosis, and died. No *post-mortem* examination was held.

Of the 9 other cases treated with excision or cautery as well, in 1 there was complete necrosis of the upper and lower eyelid, and in two others it is stated that after four days treatment of local injury was the only concern, although one was of such exceptional gravity as to have received 200 c.cm. of the serum endovenously within twenty-four hours. In another case in which the bacilli were found in the blood and urine, 190 c.cm. were administered in the course of seven days.

In the early days of treatment the doses were comparatively small, no more than 20 or 30 c.cm. being given at the initial injection. In later cases the initial dose was generally 40 c.cm., and those who have experience of the treatment strongly advocate big initial doses. In 39 of the cases the initial dose sufficed.

These cases, however, by no means exhaust the list of those in which serum treatment has been adopted. Sclavo⁸ himself in 1903 reviews the subject in a paper in which he tabulates all the cases known to have been treated in Italy whatever the stage of the disease. These total 164, with a mortality of 6.09 per cent., as compared with 24.1 per cent. for the whole of Italy. The facts stated by him he believes are very far from showing accurately the therapeutic value of the antianthrax serum. In the early days of a new treatment holding out a fresh hope, there is always temptation to use it in the most desperate cases.

To two of the fatal cases I have referred already. In the third—affecting the upper eyelid—the disease was not diagnosed until too late, when the woman presented herself with high temperature, very weak intermittent pulse, difficulty of respiration and oedema of face, neck, and chest. Death took place within nine hours of commencing treatment.

In the fourth the pulse was situated on the neck with marked cyanosis from dyspnoea caused by the oedema, running pulse; 25 c.cm. injected with little hope of benefit. Death occurred within twenty hours.

In the fifth the pustule was situated on the neck, with oedema of the greater part of the thorax. Death took place within eleven hours of admission. 20 c.cm. only were injected.

In the sixth no record was kept except that death took place within thirty hours of admission.

In the seventh the pustule was on the neck, with oedema rapidly extending to the thorax. Bacilli were found in the blood. There appears to have been no reaction to injection of 45 c.cm. on the first day, and 30 c.cm. on the second.

Of the eighth, particulars are not given except that she was admitted to the hospital in a serious condition, the victim of alcoholism and suffering from disease of the heart.

The ninth had oedema of the neck and chest, and 20 c.cm. were injected. The following day there was marked improvement; 20 c.cm. were again injected, but death occurred suddenly on the morning of the following day, with symptoms of hemiplegia.

TRIAL IN ENGLAND.

Since July, 1904, serum treatment has been tried in England, either alone or in connexion with excision, in 12 cases of external anthrax—not including 1 in which, on the tenth day when the patient was already comatose and bacilli were present in the blood, 30 c.cm. were injected four hours before death. In 4 of these serum alone was used. In No. 1 the pustule was on the malar process, in No. 2 on the forehead, in No. 3 on the upper eyelid, and in No. 4 on the forearm. The first two were treated at St. Bartholomew's Hospital.⁹ An initial dose of 40 c.cm. sufficed in both cases to arrest further "development of vesicles or other indications of the necrotic process." There was increased oedema, but this was associated with improvement in all other respects. In 1 of the cases no colonies of anthrax could be cultivated nineteen hours after the serum had been injected, although previously the fluid of the vesicles yielded abundant colonies. "Cultures were repeated on the third day, again with negative result. . . . Only a few disintegrating bacilli were found, mostly enclosed in leucocytes." In both cases

*When this was written the cases in the BRITISH MEDICAL JOURNAL of January 7th, February 11th, and in the *Lancet* of February 4th were not published.

hardly any scar was left. No. 3 was treated by Dr. Mitchell of Bradford. The patient was a mill worker. Already by the second day both eyelids were closed with oedema, which extended to the clavicle on the left side, and the right upper and lower eyelids were dark-coloured and appeared as if about to necrose. In four days 100 c.cm. were injected, 20 on the first, 50 on the second, 30 on the third, 10 on the fourth. By the fifth day the oedema had almost all disappeared except, such as would readily be accounted for by the presence of a necrotic area on the left upper and lower eyelids. Although the local symptoms were very severe the general condition of the patient remained good. Case 4 was treated at the Royal Infirmary, Bradford. The type of the disease was described as very malignant, with oedema rapidly extending to the shoulder. He received 140 c.cm. in the course of three days—30 c.cm. intravenously on the morning of the day of death. There appeared to be reaction at first in a rise of temperature to 103.6° F., but the oedema continued to spread; he became insensible, and the diagnosis of meningeal haemorrhage between the pia mater and arachnoid was made by Dr. Bell. *Post mortem* the brain was found to be surrounded with blood between the pia mater and arachnoid and nowhere else.

Six of the 8 cases in which excision was practised as well as serum administered (treated in Guy's Hospital, Bradford Infirmary, Kidderminster Infirmary,¹⁰ and by Dr. Peck of Queensbury, Bradford) made rapid uninterrupted recovery. In the seventh, treated at the North Stafford Infirmary, excision of the pustule on the hand and incisions into the brawny oedema had been made on the twelfth day of the disease. Administration of serum was commenced twenty-four hours later, when the patient was already in a comatose condition. Death took place twenty-four hours later, there having apparently been no reaction (except diminution of the oedema). In the eighth the pustule was situated on the neck, with rapidly-extending oedema. Two injections only of 10 c.cm., at twelve hours' interval, were given. Death occurred within thirty hours.

ITS CLAIMS.

The claims as to the effects of serum treatment can be summarized by saying that: (1) In very large doses it is innocuous; (2) it can be well borne even when introduced into the veins; (3) no case taken in an early stage, or of moderate severity, is fatal if treated with serum; (4) with the serum some cases are saved when the condition is most critical and prognosis almost hopeless; (5) when injected into the veins the serum quickly arrests the extension of the oedematous process so as to reduce notably the danger from suffocation which exists in many of the cases where the pustule is situated on the face or neck; (6) the serum, if used early enough, reduces to a minimum the destruction of tissue; (7) in some situations of the pustule, as the eyelid, serum must be used in preference to any other treatment; (8) persons attacked, when treated with the serum, appear to become convalescent in the course of a few hours; to these I may add (9) that in internal anthrax it is administered intravenously the only treatment which can hold out any hope.

In almost all cases injection of the serum is followed by a rise in temperature often to over 105° F., and with this there is an improvement in the general condition of the patient. The prognosis where there is this rise Sclavo regards as favourable. In the same way the necrotic process itself is to be regarded as a sign that the organism is making effort to resist the anthrax infection.

In Italy great value is attached to the treatment. A few facts may emphasize the value and importance attached to the serum treatment in Italy.

In Santa Croce,¹¹ a small town of about 5,000 inhabitants with 36 tanneries employing 350 workers, and where Dr. Cicognani has adopted the serum treatment exclusively since 1899, the workers now insist on having this treatment to the exclusion of every other, and, since operative treatment is uncalled for, present themselves when there appears the smallest pimple or boil suggesting anthrax.

Recently in Milan I visited the large-horsehair factory of Pachetti Brothers, employing some 700 workers. In addition to the steam disinfection of horsehair, a physician attends every morning to treat accidents and slight ailments, keeping careful watch for conditions or appearances suggesting anthrax. His room is fitted up as a bacteriological laboratory for verification of anthrax, a supply of serum is kept, and thus cases in the earliest stages are caught, treated, and recover without cessation of work for more than a day or two. The head of the firm states that he has no fear whatever of

the disease among his workpeople, as he has seen so many successes in dealing with it by this method. It was indeed this last piece of information communicated to me a year ago by Mr. Albert Webb, of the firm of Edward Webb and Sons, carpet manufacturers, Worcester, which led me to inquire into the method of treatment.

ITS PREPARATION.

So far I have said nothing of the source of preparation of the antianthrax serum by Sclavo, Professor of Hygiene and Principal of the Pathological Institution in the University of Siena. Its origin may be traced back to 1880, when Toussaint¹² first suggested inoculation of animals with attenuated culture as a protection against naturally-acquired anthrax. This led to the elaboration by Pasteur and Chamberland of the method which is now so largely used, especially in France.

The successful efforts made by Behring in obtaining a protective serum against diphtheria, and by Kitasato against tetanus, stimulated inquiry in a similar direction as regards anthrax by Behring, Hankin, Metchnikoff, and Roux.

Marchoux in 1895¹³ first succeeded in immunizing actively rabbits and sheep, using Pasteur's vaccines 1 and 2, and then injecting virulent cultures subcutaneously; at first in small and then in greatly-increased doses. And in the same year Sclavo, who had been working at the same subject, was able to assert from his experiments that (1) sheep brought to a high degree of active immunity could furnish a serum active against anthrax; and (2) that this serum showed prophylactic and curative power against anthrax when inoculated into rabbits. He then set to work to find a more powerful serum, and finally obtained from the ass the serum which he now uses. The result is the more curious in that, according to Behring, the strongest antitoxic serums are obtained from animals most susceptible to the organism under experiment; and to anthrax the ass is less susceptible than the goat or sheep.

Even with the ass, however, it is desirable to immunize three or four animals, and to select from among these the one producing the most active serum. In order to expedite the immunizing effect, he instituted simultaneous active and passive immunizing treatment, and finally succeeded in protecting sheep from anthrax of a very virulent nature, and satisfied himself of the curative properties of the serums by proving that 10 c.cm. administered twenty-four hours after inoculation with virulent anthrax cultures protected sheep in cases where one of the control animals died three hours and the others fourteen hours later.

He next turned his attention to treatment of malignant pustule in man, and the first case was treated in June, 1897. He desired also to test the effects of his combined active and passive immunizing method on large domestic animals—horses, cattle, and sheep; but his application to the Ministry of the Interior to defray the expenses entailed was unsuccessful, and therefore this part of his scheme could not be tried.

I have had the opportunity, through the kindness of Dr. Sclavo, of seeing all the stages in the preparation of the antianthrax serum in the Pathological Institute of Siena.

On August 10th, from an ass which had undergone the process of immunization during a period of two years, about 150 c.cm. of blood was taken from the left jugular vein. Similar bleeding had been practised on more than fifty previous occasions. On the 13th, the clot having separated, the serum was decanted, and ether was added to the extent of 3 per cent. of the whole bulk.

On the 13th, to test the efficacy of this serum, six rabbits—three to act as controls—were inoculated subcutaneously in the abdomen with 0.5 c.cm. of a suspension of a culture of anthrax (grown on agar on August 11th, and kept at 36° to 37° C.). Three of the rabbits received also at the same time 10 c.cm. of the serum injected in one of the auricular veins. All the control animals were dead in thirty-six hours with extensive oedema at the point of inoculation, and anthrax bacilli were found in the blood and tissues *post mortem*. The three rabbits which received the 10 c.cm. of serum remained well except for slight induration at the point of inoculation until the 16th, when further opportunity of observing them ceased.

The efficacy of the serum thus having been proved, the serum was then introduced with antiseptic precautions into the 10 c.cm. tubes in which form it is used.

To maintain the immunization of the ass, on August 14th 10 c.cm. of a culture of anthrax in bouillon containing 2 per

cent. gelatine was injected subcutaneously into the right and left side of the neck. This culture was made on the 13th, and was mixed with an old culture prepared in the same way a month previously. The use of gelatine in the fluid injected is believed to prevent the formation of an abscess at the point of inoculation. There was much swelling and tenderness, which had in great part disappeared by the morning of the 16th.

ANIMALS AND ANTHRAX SERUMS.

Before leaving the subject of the history of serum treatment it is desirable to state what stage has been reached in similar serum treatment of the large domestic animals because its hopefulness here appears to be as great as in case of man. This can be best done by reference to the work of Sobernheim.¹⁴

His first series of experiments were carried out in 1897 with serum of cattle which had been subjected to Pasteur's treatment, and with the serum of one cow which, after recovery from spontaneous anthrax, had been further treated by Pasteur's method. The result, so far as concerned the production of immunity in rabbits, guinea-pigs, and mice was, he considered, so variable that they were contrary to any idea of specific action of the serum. More satisfactory results were obtained from immunizing two sheep—one slowly, the other rapidly—to such a degree that they could stand enormous doses of anthrax cultures without inconvenience. The serum of the one that was rapidly immunized showed remarkable protective properties in retarding a fatal issue in rabbits for from six to eight days, but held out little hope that serum-therapy would be used as a curative agent in anthrax in animals because of the rapidity of the disease.

In a further series of experiments on sheep, however, he obtained more successful results by employing simultaneous inoculation of antianthrax serum and virus, or inoculation of each of them separately within a short interval of time. He used for the virus anthrax cultures of about the strength of Pasteur's second vaccine, believing that with this strength injurious action would not result in the presence of the immunizing serum. As a matter of fact, it was found to be non-injurious, and the immunizing effect was far greater than that obtained from ordinary serum alone.

Subsequently, to test this combined method of producing immunity, he carried out experiments over a period of two years—1900-2—with the support and encouragement of the Chamber of Agriculture of Saxony. Thirty-three sheep, 18 oxen, and some horses were treated first with attenuated anthrax cultures, and later with highly virulent cultures in increasing doses until a degree of immunity was reached so great that inoculation of enormous quantities of most virulent anthrax could be borne without material ill effects resulting. The serum and culture were not mixed together, but 5, 10, 15 c.cm. of serum were inoculated into the left side, and immediately after 0.5 to 1 c.cm. of the slightly attenuated anthrax culture into the right. After twelve to fourteen days inoculation with virulent anthrax cultures was made. The results of laboratory experiments were entirely satisfactory, as 10 c.cm. of the serum sufficed to protect, while the control animals died in twenty-four to thirty-six hours. The immunity, too, thus conferred protected 3 out of 4 sheep from contracting the disease by way of the intestinal tract. Its curative power was also shown in that of 5 sheep inoculated with virulent anthrax and then subcutaneously treated at intervals of from ten minutes to six hours later with 40 c.cm. of the serum, 2 survived, while death was delayed in the others from four to eight days. The control animals were killed in one and a half days. It was necessary to apply the method on a much larger scale in order to determine its general applicability in veterinary practice. Districts in which outbreaks of anthrax were occurring were, therefore, selected, and 2,700 cattle were treated, almost all of them by means of the combined method. No deaths were attributed to the inoculation, and no serious injury to health, even when the animals were only 2 or 3 weeks old. There was a rise of temperature and slight loss of appetite. From the moment the inoculations began cases of anthrax ceased to break out afresh. The immunity produced was lasting, as for a further nine months, up to the time of reporting, in spite of many outbreaks in untreated animals, none of the treated suffered. With larger doses animals already affected with the disease recovered.

Sobernheim feels himself, therefore, in view of these results, justified in speaking of the combined active and passive immunizing method as capable of giving powerful and lasting protection, and summarizes its advantages over

Pasteur's method as follows: (1) That it is free from danger; (2) that it is effective in one day, and has not to be repeated; (3) that a stronger dose and more active cultures are used than is the case with Pasteur's vaccine, and probably a more lasting protection is conferred; (4) that it protects from infection by way of the intestinal tract; and (5) that it can be used for curative purposes. Since then he has carried out his treatment on a large scale in South America, with results which satisfy him as to the value of the process.

METHOD OF ACTION.

I have now stated the facts as to the preparation of and the results from treatment by antianthrax serum. When attempt is made to explain its action we are still almost totally in the dark. The anthrax poison is not comparable with that of diphtheria and tetanus, because never yet satisfactorily, despite numerous experiments, has any toxin been obtained from filtered cultures of the bacillus, injection of which produces the specific effects of the disease such as are obtained from injection of diphtheria and tetanus toxins. It is customary, from its tendency to generalization on inoculation, to describe the anthrax bacillus as an exciter of septicæmic processes; but the evidence from the manifestation of the behaviour of the bacilli in the human body undoubtedly points to the production of toxin of some sort. The presence of an excessive leucocytosis at the point of inoculation, the local necrosis, the oedema, the effects extending to distant organs, and the constitutional symptoms point to such toxic action. When, therefore, we recognize the absence of toxins from filtered cultures grown in artificial media, it must not necessarily be supposed that this holds good for the life-processes of the bacillus when developing on its natural soil in the body. Further, the poverty of the blood in bacilli until immediately before death is inconsistent with the view that the extent of the symptoms is due to the multiplication of the bacilli apart from toxic production.

Sobernheim cannot speak positively on the subject. He regards the artificially-acquired immunity from use of the serum as probably due to bactericidal rather than to antitoxic processes, on the ground that the whole character of anthrax infection is septicæmic in nature, but he does not consider that specific bactericidal effect of the antianthrax serum has been definitely proved either inside or outside the animal body. The serum does not decrease the development of, much less kill, the bacilli *in vitro* any more than does normal serum, nor does it bring about definite morphological changes in them. For days and sometimes weeks after subcutaneous inoculation of large quantities of anthrax bacilli into highly-immunized sheep, the bacilli can be found at the point of inoculation. On the eighth or twelfth day after inoculation he has found them in the blood, which, in his opinion, points to the likelihood of the development of antitoxic properties.

Ivo Bandi¹⁵ states that the serum which he prepared from the sheep, and used successfully in two cases in man, possessed considerable bactericidal and antitoxic properties. To test its bactericidal power, he followed Bordet and Gengou's method of determining the presence of immune body—namely, the addition, to fresh serum containing a sufficient quantity of complement, of anthrax bacilli sensitized by exposure for some time to the influence of the specific serum heated to 55° C.

Sclavo, however, has not found that heating his serum to 55° C. for one hour in any way prevented its power of conferring immunity on rabbits.

Metchnikoff¹⁶ attributes the results to phagocytosis. The absence of phagocytosis observed by Sobernheim he explains on the ground that immunization was not as complete as in Marchoux's experiments, and consequently the conditions of negative chemotaxis were set up.

Sclavo in this connexion will not allow himself further expression of opinion than that the bactericidal substances of the antianthrax serum do not correspond in structure with those present in other bactericidal serums, and that in his experience they have only a secondary importance, notably inferior to that of the substances contained in it, which stimulate the defensive action of the phagocytes. Were the serum merely antitoxic it would not be possible, he thinks, for such differences to occur as are shown in the potency of the serum obtained from different animals. However big the doses of a weak serum, no such good results are obtained as from moderate doses of a powerful serum, probably from the fact that the weak serum insufficiently stimulates the leuco-

cytes. On the other hand, Sobernheim and Radziewsky¹⁷ found that when anthrax bacilli were introduced into the peritoneal cavity, or developed there from the spore stage, phagocytosis was present in a very small degree and at a late stage, while the swelling up and granular disintegration of the bacilli was obvious. Kiesskalt¹⁸ also tested the same point and came to the same conclusion.

The simplest explanation of these differing views is to assume the action of an intracellular toxin which in slight amounts attracts, and in large keeps back, the leucocytes. We get less confused if, dismissing phagocytosis from our minds, we still retain the idea of the cells of the body, and accept the principle of immunity to be the fabrication by these cells of the bactericidal substances which, passing into the intravascular and extravascular fluids, destroy the bacilli. Radziewsky has shown by special staining methods that all the time the development of an anthrax infection is proceeding the multiplication of organisms is accompanied by death and destruction of others. The introduction of spores of anthrax on threads into the peritoneal cavity of guinea-pigs is followed up to the ninth hour by enormous increase in number, so that a thick network of them is formed, all staining well. Between that and the eleventh hour the reverse process goes on, during which an extraordinary destruction takes place, and by the fourteenth almost all are dead. This helps much to explain the negative bacteriological find in several cases of anthrax, as the number of bacteria which may be found at the end of an infection may not correspond in the slightest degree with the number that may at one time or another have been present. If there was no formation of bactericidal substances, as the vital powers became exhausted there would be no sufficient reason to explain the decrease rather than the increase of bacilli. And it is probable that the same bactericidal substances which kill the bacillus are the same as are produced in the organism during the process of immunization.

A fatal issue in anthrax is to be explained on this view of Radziewsky by assuming that as the microbes increase so the cells of the body react to destroy them. The bactericidal substances thus produced destroy so many bacilli that the substances liberated at their death exceed the minimum lethal dose. The use of the serum, therefore, would be to assist in the destruction of the bacilli before their number was such that from their death so much poisonous substance was produced as to be fatal. If this view explained everything its use would be limited to early cases, and in late cases it might even be a direct cause of death. From consideration of the cases treated in man by the serum, we can hardly believe that its only effect is to cut short the capacity of the bacilli to increase at a time when the amount of the intracellular poison has not yet reached a lethal dose.

Recently MacFadyen and S. Rowland,¹⁹ by special methods, consisting in the use of very low temperatures, have obtained extracts from the bodies of typhoid bacilli, or in other words, their intracellular toxin. Injection of this into monkeys, rabbits, and goats over a period of four to six weeks produced a serum which showed (1) marked anti-bactericidal and antitoxic properties, and (2) curative and preventive properties as regards the typhoid bacillus and its intracellular toxin. This is the first instance where a serum has been obtained which was found to be bactericidal against a particular organism and antitoxic as regards the toxin contained in its substance.

The work of Wright and Douglas,²⁰ with its proof that the blood fluids through the opsonins contained in them modify bacteria in a manner which renders them a ready prey to the phagocytes, may be expected to throw light on the action of the antianthrax serum. The anthrax bacillus unfortunately, owing to thread formation, does not appear to lend itself well to the particular method of experimentation employed by them, namely, averaging the number of bacteria ingested by a certain number of leucocytes; but in experiments on the opsonic power of human blood in its relation to the anthrax bacillus when unheated serum was used, they say—

Although enumeration was impossible, there was everywhere evidence of phagocytosis. In the few cases where the leucocytes had not ingested bacteria, they were found to have extended themselves in a characteristic manner along the bacterial thread. Repeating the experiments with heated serum, there was practically no sign of phagocytosis.

The presence of opsonins in quantity in the blood after inoculation of serum would account for the observation of Andrewes²¹ in the case already referred to in which no anthrax colonies could be cultivated nineteen hours after injection of serum, although their presence had previously

been abundantly proved, such few disintegrating bacilli as were found being mostly enclosed in leucocytes.

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MEMORANDA:

MEDICAL, SURGICAL, OBSTETRICAL, THERAPEUTICAL, PATHOLOGICAL, Etc.

AN UNUSUAL COMPLICATION OF VARICELLA.

VARICELLA is usually regarded as little more than an inconvenience to the average subject, and complications are conspicuous by their absence. They may, however, occur, and be of a troublesome nature, an instance being described in the following note. A healthy boy of 11 slept in the same bed as his elder brother on December 29th last; the following morning the elder boy showed a definite chicken-pox eruption, and was absolutely isolated, so that no further contact of any kind or degree took place between the two. On January 13th the younger boy complained of headache, loss of appetite, and weariness; examination showed a very profuse varicellar eruption, the vesicles increasing in number for about twenty-four hours. None could be seen upon the fauces, though the throat was sore. It was a severe attack—according to the patient's account there were over 300 spots—and the general symptoms continued for two days. On the night of January 15th I was called in to see the boy, who had passed practically no urine for sixteen hours, and was in pain, with constant but ineffectual efforts at micturition. The prepuce was swollen, and its opening obliterated by a large pock, and within the urethra, half an inch from the meatus, was a very tender and painful spot, which may or may not have represented another vesicle. There was tenderness above the pubes, and at least an inch of dullness, and there was evidently severe pain referred to the hypogastrium and penis. He was at once given a hot bath and a full dose of morphine, which almost immediately induced a plentiful passage of urine. Subsequently there was a certain amount of discomfort on micturition, but not enough to call for special treatment; the swelling of the prepuce disappeared as the eruption dried up.

Curiosity led me to see whether textbooks furnished any precedent for such an unusual occurrence; in only one—Keating's *Encyclopaedia of Children's Diseases*—out of eight or nine standard English and American works was there even the barest mention of such a complication. This leads me to suppose that it is a rare incident, and therefore worthy of record.

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SCARLET FEVER IN A CHILD THREE WEEKS OLD.

I DO NOT mean to assert that this case is unique, but an undoubted case of scarlet fever in a child 3 weeks old is very uncommon. It is a good illustration of how careful one has to be in examining cases as they may be brought for quite a different complaint. This child was brought up to the outpatient department to the County Hospital, Ayr, on account of an erysipelatous condition of the scrotum and thighs. On questioning the mother it was ascertained that the child had been feverish and very fretful for two days, and had also vomiting. The legs appeared redder than usual. The child was then stripped, when the upper limbs and the whole of the body were seen to be of a brilliant red hue, the throat was very red and injected, and there was a typical strawberry