explained by Griffith on the ground that some of these lesions are caused by direct infection from the abdominal cavity, where, of course, as it is well known, the ratio of infection with the bovine to that with the human type of bacillus is high.

Significance of Numbers of Tubercle Bacilli in the Discharges from a Tuberculous Joint.

Two samples of pus from tuberculous joints which came to this laboratory attracted my attention on account of the unusual numbers of tubercle bacilli they contained. The severity of the disease turned out to be unusual also, and it seems that the numbers of bacilli in joint cases may have some prognostic significance. These cases, therefore, seem to be worth reporting.

A married woman, aged 38, was admitted to Addenbrooke's Hospital, Cambridge, on June 23rd, 1927, on account of severe pain in the left ankle. She came under the care of Mr. W. H. Bowen, to whom I am indebted for notes of the case. On admission there was a swelling on the outer side of the joint. This was aspirated five days after admission. The fluid then taken was sent to me on account of the numbers of tubercle bacilli which were visible in stained films made from it. As is well known, the bacilli in such specimens are, as a rule, either few in number or not to be seen; but in this specimen they were so numerous that it was difficult to believe that one was not looking at a rich sample of tuberculous sputum; another unusual point was that there were well-formed pus cells present. Here was a case, then, worth investigating, and I proceeded to determine the type of the tubercle bacilli.

The clinical course of the case showed a disease of great activity. The history on admission was seven weeks only, and consisted chiefly of severe pain in the left ankle, especially at night. The joint appeared to be exquisitely painful on the only occasion that I saw the patient. Soon after admission it was immobilized on a poroplastic splint; but seventeen days later it was necessary to aspirate again, and 20 c.cm. of caseous fluid was then removed. The disease progressed rapidly, and it became imperative to amputate the limb. This was done forty-four days after admission. But though the wound healed the condition of the patient did not improve. On the contrary, she rapidly went downhill, and died of meningitis on November 11th, seven months after symptoms had first appeared in the joint. Tubercle bacilli were found a few days before death in cerebro-spinal fluid removed by lumbar puncture. Mr. Bowen writes: "The outstanding feature of the case was the rapidity of the process; also very noteworthy was the persistence of pain in the joint."

After death there were found marked signs of cerebral tubercle: excess of fluid, flattening of convolutions, tubercles in the basement membranes, dilatation of ventricles. In both lungs were some old fibrous scars at the apex, and here and elsewhere recent foci commencing to break down into little cavities with caseous walls; in the rest of the lung tissue diffuse miliary tubercles. A few minute tubercles were seen on the surface of the liver, but none in kidneys or spleen. The mesenteric glands and peritoneum were normal. The bronchial glands were much enlarged and beginning to show small caseating foci.

The original sample of pus, so rich in tubercle bacilli, had arrived in my absence, and I was unable to deal with it. Three weeks later I obtained a second, in which tubercle bacilli were present, but not in anything like the numbers originally seen, and pus cells were now absent. From this sample animals were inoculated and a culture raised from a tuberculous guinea-pig. The culture grew luxuriantly, and formed voluminous nodular growths on glycerin-potato and glycerin-agar, and, on suitable batches of glycerin-serum, it produced a yellow growth.

Four rabbits were injected intraperitoneally with 10 mg. of bacilli from young serum cultures. They were killed about four months later, fat and well grown. With one exception the lesions did not exceed those usual after such an injection of tubercle bacilli of human type—namely, a few little lightly encysted collections of caseo-purulent matter in the peritoneal cavity; but in one animal paralysis of the hind legs had occurred, and at the *post-mortem* examination a tuberculous lesion was found in one of the vertebrae, pressing on the spinal cord. Such a lesion is not unknown after injections of tubercle bacilli of human type into the rabbit; both Griffith and myself have met with it, and its presence in this case in no way weakens the conclusion that the bacillus with which we were dealing belonged to the human type. This strain of bacilli has since been used for many other experiments having a different object, and it has all along shown that low degree of virulence and inability to produce a progressive disease in the rabbit which is characteristic of the type. For the guinea-pig it proved virulent, and caused fatal tuberculosis.

The second case was that of a tuberculous wrist-joint in a man aged 69 years. As in the other case, it was the tubercle bacilli in the pus from the joint that first excited my interest in it; but they were not so numerous as in the first sample from that case. Some were seen in most of the fields; the largest number seen in any one field was five.

For the clinical history I am indebted to Dr. Christopher Tylor of Long Melford, Suffolk. The disease in the joint came on after a slight injury caused by jarring it severely when using an axe. About the same time the patient developed a cough, and had physical signs indicating tuberculous mischief in the lungs. The disease in the wrist-joint then became more acute, and there was evidence of fluid. Six months after the commencement he was sent to Addenbrooke's Hospital, Cambridge, where an operation was performed by Mr. Cooke, who let out a large quantity of pus, curetted the walls of the abscess cavity and the bones, and closed the wound without drainage. A few days later the patient returned to his home. After this the pulmonary disease advanced rapidly, and he died a few weeks after his discharge from the hospital. No *post-mortem* examination was made.

A culture raised from a guinea-pig inoculated from the pus showed all the characters of the human type, and produced voluminous nodular growths on glycerin-potato, wrinkled films on glycerin-agar, and pigmented growth on certain batches of serum.

Two rabbits inoculated intraperitoneally with 10 mg. of serum culture on September 22nd remained well, and when killed two months later were well-grown, fat animals, with no sign of tubercle beyond the usual little collections of caseo-purulent matter lightly encysted in a thin membrane (which one so frequently sees in the peritoneal cavities of rabbits injected with the human type of bacillus), and in one of the animals a little wedge-shaped streak of chronic tuberculous disease in one kidney.

There can therefore be no doubt that in this case, as in the other, the tubercle bacilli concerned were of the human type, and we may conclude that the fact that numerous tubercle bacilli are visible in stained specimens of pus from tuberculous joints is not inconsistent with an infection caused by bacilli derived from another case of human tuberculosis.

The unusually rapid course and the fatal termination in these two cases, selected only because there were large numbers of tubercle bacilli visible in the discharges, raise the question whether the presence of these bacilli in numbers such as these cases showed would justify a grave prognosis. One hesitates to draw this conclusion from two instances, but they at least call for further observations of cases of a similar kind.

REFERENCE.

¹ *Bovine Tuberculosis in Relation to Man*. Published by the National Clean Milk Society, 1923.

EARLY DETECTION OF TUBERCLE BACILLI IN SPUTUM:

PRACTICAL METHODS OF OBTAINING SATISFACTORY
SPECIMENS.

BY

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THE importance of the early detection of tubercle bacilli in the sputum has been most strongly insisted on by Dr. Chandler and by various correspondents in recent issues of the *British Medical Journal*. I can heartily endorse their views, and I propose, therefore, to describe some very practical means for applying them in cases of difficulty such as not infrequently present themselves.

In many of these cases in which the general clinical evidence is in favour of the diagnosis of tuberculosis the report on the sputum supplied by the patient is that no tubercle bacilli have been found. As often as not this is because a good specimen of the sputum has not been obtained. Many patients seem to be unable to eject the liquid from the bronchi, but involuntarily swallow and spit little more than frothy saliva from the mouth. By means of *coaxing*, and urging them to "shoot it out into the bowl" while the head is kept down over it, a better specimen may often be obtained. If this fails, an active cough reflex may be excited by getting the patient to sniff

the vapour of *oleum sinapis volatile* from the neck of a bottle (say a six-ounce medicine bottle) at the bottom of which there is about half an ounce of the oil. This gives off the vapour all the more readily if the bottle is warmed over a lamp. Two or three sniffs generally result in a good cough and the expulsion (with a little encouragement) of the ejecta from the larynx and trachea into the basin. The sister in charge of the throat room at Brompton Hospital is of the opinion that if this does not excite a cough there is probably no laryngeal tuberculosis. I cannot go quite so far as this, but I am sure that the procedure described has often given us a "positive" result when all previous examinations had proved "negative." In a recent case a history of syphilis led to a diagnosis of that disease as the cause of the hoarseness which was complained of, no bacilli having been found, but a sniff of the oil led to a cough and the expulsion of a small quantity of sputum, in which the bacillus was found in fair abundance. This procedure should, of course, not be preceded by anaesthetization of the nose or larynx.

Another method of value when by any chance the former fails is the *intralaryngeal injection*, by means of a syringe, of a few drops of the lotion we use for cleaning up the larynx—namely, a weak solution of sodium bicarbonate to which is added a little hydrogen peroxide. This is done under the guidance of the laryngeal mirror, and it often works well, but in some cases we are balked by the obstinate closure of an irritable larynx.

In a case of this kind I recently tried another process. The patient either could not or would not cough, and

failed to respond to the methods above described. I therefore applied to his case the principle of *transnasal instillation* used for the introduction of oily solutions into the larynx. The patient was seated with his head thrown back and his mouth wide open. He was instructed to pant in and out through his mouth and not to swallow. While he was doing this I gently syringed about half a drachm of the soda and peroxide solution drop by drop through the nose. A small quantity entered the larynx and started a cough which resulted in the expulsion of a little sputum into the basin. Tubercle bacilli were found, and the diagnosis established. The patient was not upset in the least, and reported himself later as feeling much better.

I have occasionally caught on the *laryngeal mirror* a little patch of sputum sufficient for staining purposes, if the patient coughed spontaneously or did so by instruction during the examination. The examiner does well to wear a muslin veil when practising this last method.

The administration for a few days of *potassium iodide*, if not otherwise contraindicated, is known to facilitate the expulsion of sputum, and my colleague Mr. Ormerod and I have made use of it for this purpose.

These processes have helped in many cases of doubt or difficulty, and I describe them in the expectation that others will find them useful. It need hardly be said, however, that they should not be practised without discrimination. The most appropriate cases are obviously those in which there is doubt as to the diagnosis, and in which, therefore, the disease has not reached an advanced stage.

THE RESISTANCE FACTOR IN DISEASE:

WITH SPECIAL REFERENCE TO SEPTICAEMIA AND ALLIED CONDITIONS.

BY

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In January, 1927, I was called into consultation in a case of facial erysipelas. The patient, who was *in extremis* and who died some six hours later, appeared to have been an otherwise healthy and abstemious man, and his death drew attention to the unsolved problem: What is the true or chief factor in causing the death of a patient who is suffering from a septicæmic condition? The question was put to several medical colleagues, and the answers were interesting, if not very illuminating. One man replied that the cause of death was a profound toxæmia; another, that the centres in the brain were put out of action by bacterial toxins; a third gave it as his view that death was due to cloudy swelling of all the cells of the body; a fourth answered that he did not know, and a fifth suggested that death was due to a lack of resistance on the part of the patient.

Such diversity of opinion indicates the difficulty of the question at issue, and although we may theorize as to the cause of death, the majority of us must admit frankly that we can offer no certain explanation of it. But we are on safe ground when we say that death has resulted from the patient's lack of resistance to the effects of bacterial invasion. This is, of course, a self-evident fact. If his resistance had been all-sufficient, it is unlikely that he would have died.

"The patient seemed to have no resisting power" is a phrase that we have used, often wonderingly, when a previously healthy man has succumbed to some infection—when he has been poleaxed, so to speak, by a disease from which he might reasonably have been expected to recover. Six men may have lobar pneumonia, and one—often seemingly the healthiest prior to the illness—may die, while the remaining five recover. Or death may occur unexpectedly following an apparently successful operation for appendicitis, or from septicaemia following a normal childbirth in which no manual or instrumental interference was required.

What is this lack of resistance, this subtle x factor, which determines a dangerous downhill course or even a fatal issue?

I desire to put forward the hypothesis that our successful resistance to bacterial infection depends largely on the orderly response of certain of our endocrine glands—namely, the sympathicotrophic group comprising the thyroid, suprarenal, and pituitary, and the vagotrophic group comprising the parathyroids and the pancreas.

EXPERIMENTAL CONSIDERATIONS.

Extirpation of the thyro-parathyroids produces a reduction in the phagocytic properties of the leucocytes in a normal man; extirpation in monkeys produces increased liability to infection, and in some animals there is frequently a fatal result.¹ Extirpation of the suprarenals appears to be invariably fatal. With regard to the pituitary Cushing² states: "My own impression has been that total extirpation often provokes a peculiar train of symptoms passing from cachexia to coma and ultimate death." Smith³ says that if the pituitary gland of rats is sucked out by the buccal route an invariable syndrome occurs. In young animals there is cessation of growth, and in adult animals there is, *inter alia*, physical impairment with atrophy of the thyroid, parathyroids, and suprarenal cortex.

Since extirpation of one or other of these glands may produce such serious results, surely it is only sound common sense to assume that a severe infection in the blood stream, attacking each and every gland simultaneously, may produce a result which may easily be fatal. To swamp an endocrine gland with a potent toxin must surely cripple its function, sometimes to an extent which may be equivalent to extirpation.

In profound toxæmias or infections in childhood hæmorrhage may take place into the adrenal medulla, producing profound collapse, associated with convulsions, vomiting, and purpura, a fatal result generally occurring within twenty-four hours.⁴ Elliott and Tucker have shown the lack of chromaffin substances in the adrenals of fatal cases of diphtheria,⁵ and, in certain fulminating cases of cerebrospinal meningitis, hæmorrhage into the suprarenals has been associated with the fatal termination.

Unless the infection is overwhelming in potency, the glands may withstand its effects to some extent and for some time, and may hold out until the invasion has been quelled successfully. But in certain individuals what appears to be a comparatively mild disease may be fatal, and I suggest that the following are among the explanations in many such cases.