A NEW FORM OF TUBERCULIN (T.F.) SOME NOTES ON ITS DIAGNOSTIC AND THERAPEUTIC VALUE.

BY W. C. LYONS, M.B., CH.B. EDIN.,

SENIOR ASSISTANT MEDICAL OFFICER, UNION HOSPITAL, BRADFORD.

IN applying the various tests with old tuberculin for the diagnosis of tuberculosis one is struck by the comparatively large number of patients reacting positively in whom no trace of tuberculosis is found clinically, and who give no history of a tubercular infection.

In a series of 15 post-mortem examinations on patients who at times varying from one to two months before death gave a positive reaction, both with the vaccination and blister methods of applying old tuberculin for diagnosis, six were found to be tubercular subjects. Of these, three proved to have pulmonary tuberculosis, while one had lesions of tubercular peritonitis, the lungs being healthy. In one case a healed lesion was demonstrated at one apex, and in another caseous glands of the neck were found. In the remaining nine cases no obvious tubercular disease was discernible, special attention being directed to the bronchial, mediastinal, and mesenteric glands, lungs, and meninges.

One case which yielded a positive reaction with both the vaccine inoculation and blister tests was very instructive. A male, aged 46, was admitted suffering from pulmonary tuberculosis. The usual clinical symptoms were present, but tubercle bacilli were never demonstrated in the sputum on repeated examination. On examination the right lung presented a localised area of dullness, with moist sounds and a prolonged expiratory murmur. It was accordingly diagnosed as phthisical. The condition rapidly changed, and a few weeks later, on development of further signs, malignant disease of the lungs was suspected. At the necropsy this view was confirmed. The right lung and bronchial glands were found to be infiltrated with areas of carcinoma, and, further, no obvious trace of tuberculous disease was found.

In investigating this subject it was thought that old tuberculin might contain some substance which produced a positive reaction, perhaps by irritation, on apparently healthy individuals, whose skin is not sensitised by the products of the tubercle bacillus, and if that substance were removed a positive reaction would more definitely indicate the presence of tubercular disease.

On adding to 10 c.c. of old tuberculin 60 c.c. of absolute alcohol a cloudiness appears in the solution, which on standing for 24 hours settles as a precipitate which clings to the sides of the vessel. The supernatant liquid is again precipitated with absolute alcohol and filtered. The precipitate from both precipitations is dissolved in 10 c.c. of distilled water. This solution is again precipitated and filtered; the filtrate obtained from this is added to the first filtrate, and the whole evaporated to its original bulk (10 c.c.) at a temperature of 56°C.

The combined precipitates are dissolved in 10 c.c. of distilled water. The resulting solution contains the same amount of precipitate as the original 10 c.c. of old tuberculin. The solution of the precipitate is diluted with distilled water to form a 10 per cent. solution. If now 1 minim of this 10 per cent. solution of the precipitate is injected under the horny layer of the skin in three or four hours a small, raised, inflammatory area about half an inch in diameter appears around the site of injection in about 92 per cent. of all cases, both tubercular and apparently healthy individuals. This reaction, therefore, proves of no particular value in diagnosis.

The filtrate which has been evaporated to its original bulk is now taken and diluted with distilled water to form a 10 per cent. solution. If 1 minim of this solution be injected under the horny layer of the skin, a raised inflammatory area appears round the site of injection in from 12 to 18 hours in known tuberculous individuals; no positive reaction has been noted in persons apparently free from tuberculous disease, such individuals being likewise free, according to their clinical histories, from any suspicion of tubercular affections.

In applying the 10 per cent. solution of the filtrate for diagnostic purposes the procedure is as follows. A small area of the skin of the forearm is cleaned with soap spirit and rendered tense, as one does when vaccinating; the point of a

hypodermic needle is then inserted obliquely between the horny and Malpighian layers, the aperture of the needle being turned towards the surface. One minim of the solution is then injected; a control of distilled water is injected in the same way. On withdrawing the needle some of the injected fluid escapes and is removed on a piece of cotton-wool. No dressing is required.

A positive reaction is seen to be as follows. Around the site of injection a raised area of inflammation and induration appears in from 12 to 18 hours. The inflammatory area in early cases of tuberculosis is usually nearly an inch in diameter, the edges gradually fading to normal skin. The area of induration is noted in the immediate vicinity of the needle prick. In more advanced cases the inflammatory area is smaller, usually about half an inch in diameter, the edges being more sharply defined. In these, too, the area of induration is well defined round the needle prick. In still more advanced cases the area of inflammation and induration is less well defined but recognisable, while in very advanced cases a reaction, if at all present, is only very slight. In early cases the reaction persists for three or four days, while in advanced cases it passes off in from 24 to 48 hours.

The test as described has up to the present been applied to 270 persons. Of these 191 were known to be suffering from tuberculous disease in various forms. Of these 191 tubercular cases the reaction was positive in 186; the 5 tubercular cases yielding a completely negative reaction were in the last stages of pulmonary tuberculosis and died within two weeks of the date of application of the test. In the remaining 79 negative cases no reaction whatever was noted, and in these great care was taken to exclude the possibility of a tuberculous infection past or present.

The reaction given by the filtrate has up to the present been found to have great value in assisting in the diagnosis of medical and surgical cases of tuberculosis, and especially so in cases of incipient phthisis otherwise in doubt.

Therapeutics.—A number of patients have been treated with the filtrate (for convenience termed T.F.), and so far the results have been very encouraging. The initial dose found to be most convenient is 0.001 c.c. This is increased every other day by from 0.0002 c.c. to 0.001 c.c. according to the reaction produced. It is easily borne and does not produce the untoward results so frequently given by other forms of tuberculin. The reactions by the patients are, as a rule, slight. There may be two hours after injection a slight rise of temperature, seldom more than 0.6° F., and this usually becomes normal in ten hours. In some cases for about two or three hours a slight headache or feeling of malaise or pain near the site of injection is complained of, and this usually completely disappears in a few hours.

The remedy seems to have a beneficial effect on the temperature, which in about one-third of the cases treated was swinging and "hectic," became normal in a week, and remained so during the course of treatment. As a rule, over the site of the injection there appears a small swelling which passes off within 24 hours.

It has been customary to select the supraspinous fossa as the seat of injection. The skin is first painted with tinct. iodi, and the injection made deep into the muscle with a platinum needle. Alternate shoulders are chosen to receive the injection every other day. Thirty cases of pulmonary tuberculosis have up to the present been treated with T.F. for two months and all have benefited thereby, as evidenced by the fall of temperature, increase in weight, disappearance or diminishing of the moist sounds in the chest, and lessening or disappearance of the cough, as well as a feeling of well-being expressed by the patients.

A typical case selected from the 30 cases treated is as follows. A male, aged 14 years. Admitted Sept. 9th, 1912, suffering from pulmonary tuberculosis. The usual symptoms, cough, loss of weight, and night sweats, were complained of. On examination well-marked signs were discovered in the right upper and middle lobes, and some moist sounds and prolonged expiration in the left apex. Weight 5st. 10lb., temperature swinging from 97.2° to 100° F., with several reverses. Treatment was commenced on Sept. 12th; within a week the temperature became normal and remained so ever since. Patient was given increasing doses of T.F. every other day. On Oct. 30th all the moist sounds in the chest had disappeared. Weight 6st. 10lb. Cough has quite disappeared and there are now no night sweats.

Union Hospital, Bradford.

AN INTERESTING CASE OF ARRESTED TUBERCULOSIS (?)

By CHARLES GAYFORD, M.D. DURH., M.R.C.S. ENG.,
L.R.C.P. LOND.

THE patient, aged 51, actively engaged in his professional work, who has been under observation for fully 20 years, went for a holiday in August, 1911. With his family he spent a month at a select and well-known resort on the East Coast. During this time he contracted what he called a severe cold, and he came home again with its effects increasingly troublesome, and consulted me. He had at that time an almost constant cough, considerable expectoration, some fever, restlessness, night sweats, loss of weight, and loss of strength. Any ordinary effort was enough to throw him into a state of general free perspiration; even the act of undressing for the purpose of examination of his chest did this, for beads of sweat trickled off him while under this ordeal. His heart was found to be normal, as was the pulse, except that its frequency (96) indicated that something abnormal was at work. Examination of the urine revealed nothing abnormal in the renal organs. The lungs were also found to be perfectly normal except the upper portion of the right lung. From the level of the third rib in front to the apex, and again at the back from the level of the infrascapular fossa of the scapula upwards, there was evidently infiltration and a considerable consolidation of the lung. Scanty moist râles were present over this area, with bronchial breathing, which was most marked. Under treatment the cough disappeared, the expectoration ceased, the temperature became normal, the sweats passed off, and his strength returned. His weight also went up to his usual point. The sputum (at the time he was expectorating) was examined at the clinical department, St. Bartholomew's Hospital, and no tubercle bacilli were found. He continued his work, and through a trying cold and damp winter he suffered no relapse, though frequently exposed to all kinds of climatic conditions, some very adverse. But notwithstanding all this, the lung did not clear.

The history is as follows. At 10 years of age he is said to have been the subject of a severe attack of tuberculous peritonitis. His mother, who is hale at 88, told me that her son was so ill that no one expected he could live. The doctor in charge told her that nothing more could be done for him, and she must be prepared for the worst. He survived, and after a protracted convalescence he slowly recovered his health. Till 14 years of age he scarcely grew at all, but after that he shot up, and he now stands 5 ft. 10½ in. in height. As a boy he was dark in complexion, and therefore no one noticed whether he got darker and more bronzed after his illness than he was before. The presumption is that this was the case. To this point I shall return after the narration of his subsequent history is completed. From his fourteenth year onwards his health has been good. Except for colds, rheumatism, neuralgia, occasionally, on no occasion had he had to stay away from business. Five years ago he had a lump form in the left ischio rectal fossa, which came to a head and burst externally. But that did not entail sufficient suffering to induce him to tell me anything about it, though he came to see me from time to time about other minor ailments. This lump has hardened from time to time, then burst again and got easy, but never gave more than a passing inconvenience, and it was only quite incidentally that he mentioned (some three or four months after I had been treating him for his lung trouble) "this trouble below," which led to the discovery that he had fistula. Mr. C. B. Lockwood saw the patient with me in January last, and advised immediate operation. Owing to the pressure of business engagements that course was postponed till July, when Mr. Lockwood laid the sinuses bare and excised them. It was quite remarkable to notice how the condition of persistent lung infiltration responded to the paroxysmal hardening and tightening of the ischio-rectal lump, and again showed signs of clearing after a fresh discharge relieved the discomfort of the fistula. A suppository

containing gr. iii. of potassium formate was ordered, and under the influence exerted by this means the sinus remained quiescent and did not fill again. But the condition of the lung persisted and Mr. Lockwood suggested that it might be desirable to get a vaccine made from the discharge from the sinus and try its effects upon the lung tissue involved. For this purpose Dr. F. W. Andrewes was consulted. But at the time there was no discharge obtainable even with an aspirating needle. Consequently we decided to have all the tissues, the sinuses, abscess sac, &c., removed at the operation sent on at once for pathological examination, and from them to prepare a vaccine for use if need be.

Dr. Andrewes's report upon the further examinations of the patient's sputum and the tuberculin test he carried out subsequently is as follows:

The specimens of sputum supplied contained no tubercle bacilli, and appeared from its characters to be largely of pharyngeal origin. I carried out a von Pirquet's graduated test, using old tuberculin pure and diluted 4, 16, and 64 times with a control spot. The patient gave a moderate reaction with the pure tuberculin and that diluted fourfold; the reaction was slightly more with 16-fold dilution, and very slight with the 64-fold dilution; with these the normal man scarcely reacted at all. The result of the test was thus somewhat equivocal, but I should consider it as pointing against any active tubercle at the present time. It is a reaction such as I should expect a man to give who had formerly had tubercle.

The date of this report is June 14th, 1912. On July 19th Mr. Lockwood operated, and the sinuses with such parts of the surrounding tissues as were removed was at once despatched in a sterilised bottle to Dr. Andrewes for examination. His report of this is given in his own words:—

I have now microscopic sections through the piece of tissue removed. I can only find scar tissue. There is no evidence of any active tissue infection, and I cannot find any sign of tubercle.

The operation itself afforded evidence of a very suggestive character which pointedly illustrates the probable nature and mode of origin of the fistula. In shape it formed an irregular Y-shaped figure, and the two arms of the fistula which passed off at irregular angles from the main arm, which opened upon the surface, made their way to the wall of the rectum. On laying open the main arm the probe passed easily along each of the other arms and entered the rectum at different levels, the one just inside the internal sphincter, the other higher up. They were all excised and the openings into the bowel closed with stitches. The patient made an uninterrupted recovery. But the infiltrated segment of the right lung still persists.

There are two or three other points of interest. In the first place, sepsis was mentioned as a possible source of the lung mischief. The sufficient negation of that hypothesis lies in the fact that after complete removal of the fistula, which was the only obvious seat of septic poison, the infiltration of the lung tissue continued unaffected. Though while the fistula remained active the lung repeatedly responded to the paroxysmal exacerbations of the fistula, the infiltration remained undiminished and unaltered after its removal. Therefore another source of the mischief must be sought. Sir Dyce Duckworth, when consulted by me on this interesting case and before the fact of the presence of fistula was known to me, quoted the dictum, "Once tubercle always tubercle." And it is a question of great moment in this case: as to whether or not the evidence it carries does not warrant the belief that this patient still carries about within him the seeds of tubercle, notwithstanding the fact that these sporadic forms of tuberculous activity aborted. For I certainly conclude that the attack of five years ago, which resulted in fistula, was of the nature of tuberculous ulceration in the rectum, and as certainly do I conclude that the attack of lung infiltration and invasion in the summer of 1911 was another active manifestation of tuberculous activity. In the original attack the retroperitoneal glands became the prison-houses in which myriads of tubercle bacilli were incarcerated and encysted. The general tissue resistance he then manifested shows that phagocytosis was in him so effective that all other tissues were cleared of tubercle. So complete has the maintenance of the investment of these imprisoned bacilli been that for fully 35 years none of them escaped. Five years ago a detachment of them did effect their escape, and they were responsible for the ulceration in the rectum and the consequent fistula. A year ago some others escaped and effected a lodgment in the apex of the right lung. But so vigorous has been the maintenance