had been heard was somewhat increased, and the crepitant *rales* had become much louder, coarser and moister.

In another case in which I injected 2 milligrammes, the patient had only just had a severe attack of hæmoptysis, and it was thought by some that the injection might provoke further hæmorrhage; but, on the contrary, the expectoration became freer and more mucous, and without any appearance of fresh bleeding.

Nothing to me is more remarkable in connection with this treatment than the feeling of subjective amelioration which so constantly follows these strong reactions in cases of advanced disease.....

Relapses.—Finally, there is the question of relapses. I suppose there is no doubt that cases of lupus have already relapsed, but this, it seems to me, was to be anticipated. It is too much to expect that with one course of treatment extending over a few weeks only, a disease like tubercle is to be wholly eradicated from the body. Koch himself appears to have expected that relapses would occur, and that a reapplication of the treatment would be in many cases needed.

PERSONAL IMPRESSIONS OF KOCH'S TREATMENT AT BERLIN, WITH EARLY NOTES OF CASES TREATED IN THE ROYAL INFIRMARY OF EDINBURGH.

Read before the Medico-Chirurgical Society of Edinburgh, December 3rd, 1890,

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I HAD proposed to-night making a communication regarding an extended research into the local therapeutics of the respiratory apparatus. But the publication by Dr. Koch on the 14th November of "A Further Communication on a Remedy for Tuberculosis," and the opportunities afforded by a visit of ten days to Berlin for studying the results obtained, have led me to delay the other in favour of a summary of the impressions produced by this visit. If these should appear imperfect or disjointed, I beg you will allow the short time which has elapsed, and the press of work during the few days since my return, to be the excuse.

I have had an opportunity of observing, more or less fully, some 200 cases in different hospitals, and what I have to say is based entirely upon my personal notes. I take this opportunity of testifying to the courtesy and kindness displayed by the physicians and surgeons in charge.

The fluid—of which, through the personal kindness of Dr. Koch, I have been able to bring home a small quantity, and of which I show you a few drops, is transparent and of brownish colour, resembling an East India sherry. Of its chemical constitution little can be said definitely. But from statements made by Dr. Koch to his Excellency Herr von Gossler, the Minister of Education, and other incidental references, it is probable that it contains one or more of the chemical resultants from the growth in given media of the tubercle bacillus. From what I learned at the Hygienic Institute, it is clear that the process of elaboration and separation is difficult. Koch has stated that it would take months for a good worker to become thoroughly familiar with the method of preparation. This, along with the necessity for uniformity of strength, explains the apparent delay in the distribution of the fluid. There seems every likelihood that, meanwhile, the German Government will keep the preparation and distribution in its own hands.

In its undiluted state, the fluid may be kept indefinitely without change. But when diluted for injection—as it is, usually, with distilled water—it is liable to decomposition, the fluid becoming turbid. This difficulty may be overcome by diluting with a half per cent. solution of carbolic acid. Boiling causes no precipitation, but the addition of alcohol does.

For injection it is generally used in solutions of 1 to 10, or 1 to 100, or 1 to 1,000. The proportion of the solution is, of course, of less importance than the actual dosage. For most internal conditions, such as phthisis, empyema, etc., the treatment is commenced with 0.001 gramme (in delicate patients and children, it may be, with 0.0005 gramme). Comparatively early a relative tolerance is established, and the dosage is increased gradually up

to 0.01 gramme or more. For more superficial conditions, such as lupus, tubercular adenitis, articular tuberculosis, etc., the dose begins usually at 0.01 gramme for the adult, and this is gradually increased up to, say, 0.1 gramme. The rate of increase I found to vary considerably in the hands of different operators and with different patients.

The fluid is introduced subcutaneously. It has apparently no action by way of the stomach. Fräntzel and others have tried its introduction by way of the respiratory passages; but while it was found to be operative, greater difficulty was experienced in regulating the dosage. The seat of injection is quite independent of the seat of lesion. That selected by Koch (at first for convenience, and that the patient might not know what was going on), in the loose fold between the shoulder blades or in the lumbar region, is usually adhered to, though I have frequently seen the injection made into the leg and arm, apparently with equally good result. The instrument in general use is Koch's bacteriological syringe. It has been sufficiently described in the medical papers, so that I need not enter into details regarding it. For rapid clinical work it has disadvantages, which can, in my judgment, be avoided by the use of one of the recently perfected hypodermic syringes, without any risk of harm to the patient, if cleanliness be properly attended to. Already in some of the clinics other syringes are in use. Meanwhile, in the Royal Infirmary, I have preferred to continue Koch's syringe and rigidly to follow all his instructions till the method be fully tested. The injection is practically painless. I have never seen local disturbance occur at the seat of injection, saving slight pain when the patient happens to be percussed over the point of entrance of the needle, it may be on the succeeding day.

Effects of Injection.—On a healthy subject, that is, a non-tubercular subject, injection of so comparatively large a dose as 0.01 gramme produces practically no result. There may be passing, hardly appreciable, *malaise*, with, perhaps, rise of temperature to 100° F. To produce serious symptoms on such a subject, so large a dose as 0.25 gramme is required, as tested by Koch in his own person, when three to four hours after injection there supervened pain in the limbs, fatigue, inclination to cough, and difficulty in breathing, which speedily increased. In the fifth hour a prolonged rigor ensued, and, about the same time, sickness, vomiting, and rise of temperature to 103.8° F. After twelve hours these symptoms abated. The temperature fell till next day, when it was normal. A feeling of fatigue and pain in the limbs continued for a few days, and the site of injection remained similarly slightly painful and red.

In most of the cases of lupus which I saw treated the dose was commenced with 0.01 gramme, except in case of children, or when, in addition to the lupus, there was evidence of other tubercular processes. If internal processes, pulmonary or otherwise, complicated the case, the dose was that given for internal cases. With such a dose, 0.01 gramme, in practically every case results of a most striking character ensued, conveniently divided into general and local.

General Reaction.—This begins to be manifest from four to six hours after injection. It consists in the onset of fever—the temperature rising, often rapidly, to from 102° F. to 105° F., or even higher. Associated with this there is an increase in the pulse rate and in that of the respiration, the latter, as a rule, relatively greater than the former. In one case, where, however, there was undoubted lung complication, and the patient had a correspondingly smaller dose, the respiration became 60 per minute at the height of the reaction. (I have also seen this rate attained in a case under treatment in the Royal Infirmary of Edinburgh.) The patient lay panting for breath, but was not so livid or otherwise disturbed as when a corresponding rate occurs, say, in croupous pneumonia. The pulse, while rapid, was fairly full and perfectly regular. Associated with the increase in respiration, and sometimes apart from it, there is coughing, often troublesome, accompanied, in many instances, by expectoration, even when there has been none previously. Sickness, vomiting, and general *malaise*, of varying degree, occur. In some instances diarrhoea was noted. In some dozen cases I saw a distinct exanthem—something between a roseola syphilitica and measles, but in others more papular. (I have seen this occur twice in the cases I have since injected at Edinburgh.) In a fair proportion of cases an icteric tinge of the skin was distinctly evident. A few appeared to be unusually pale.

More serious manifestations consist in loss of consciousness and delirium (which I have seen at least a dozen times in young children at Berlin and once in Edinburgh), followed by a condition of som-

nolence, lasting many hours it may be. In some instances, the somnolence occurred apart from the other cerebral condition. In a few instances epistaxis was noted.

As a rule, the general reaction begins to decline at the end of twelve hours or so; sometimes, in one or other manifestation, it continues for twenty-four hours or longer. The complete cessation of general symptoms affords a guide to the desirability of repeating the injection. Often a day or two, it may be longer, is allowed to elapse before the second injection. The remarkable feature, *quâ* the general reaction, is that a repetition of the same dosage produces generally distinctly less serious results.

The *local reaction* is best studied in lupus. It becomes manifest, with practically absolute certainty, in the affected area or areas, wherever situated. It appears at a varying period from six to twelve hours after injection, and consists in swelling—the nose, for example, becoming two or three times its normal size—and redness of the diseased part. A zone of redness of varying breadth also surrounds the lupus area and, in well defined cases, a whitish ring immediately within the red zone is distinctly traceable. This is often preceded—it may be some hours—or accompanied by a subjective feeling of tension and burning. A slight exudation soon begins to ooze from the surface, the yellow drops of which run together, dry, and form crusts. This incrustation grows in thickness, until it tumbles off in, perhaps, a week or ten days (in one case in the Royal Infirmary part of the scab began to break up shortly after the second injection). Sometimes pus tends to collect below, and it is convenient to loosen the crust to afford free vent. This may easily be accomplished by the use of oil or other softening agent. In many cases where it was allowed to fall off naturally, I have seen it disclose a smooth, delicate surface of pale red colour. In the cases where I saw it picked off, the sore presented the appearance of a granulating surface.

I have seen some six or eight cases of lupus to all intents and purposes cured after from six to ten injections. The frequency with which the injections are repeated I have found to vary with different operators. Koch, in his original statement, speaks of allowing the reaction after the first dose to come to an end entirely, and, after a week or two, again injecting 0.01 gramme; but at some of the hospitals the dose was repeated more frequently, the time being fixed by the general state of the patient, and, particularly, the disappearance of all signs of general reaction.

In connection with lupus, it is most interesting to note that the local effect is not confined to the place evidently affected. I have seen this frequently illustrated. I have seen swelling and redness appear at points—perhaps in the extremities—where no lupus had been observed or suspected. After one or two injections patches of lupus have made their appearance, as if the tubercle nodules were lying latent, too deeply buried to be noticeable, till accentuated and brought to the surface, as it were, by the specific. Further, several patients with lupus have, after injection, complained distinctly of pain in one or other joint, or a gland has become definitely swollen, suggesting that a focus of tubercular disease was present where it had not been possible to diagnose. Further, in one or two cases, local changes in the chest, subsequent to treatment, suggested that pulmonary tuberculosis, hitherto undetected, was present—a fact to which, perhaps, the supervening sputum pointed. It must, however, be borne in mind that sometimes this last symptom developed after injection in apparently healthy persons.

Before leaving lupus I should add that I have seen several cases of lupus affecting the mucous surfaces of the palate, pharynx, and tongue react in a similar way, and show a similar tendency towards cure.

Glandular conditions are treated in the same way; the general reaction need not be described again (see above). The local reaction manifests itself frequently by increased swelling, which continues for twelve to twenty-four hours or longer, with perhaps an accession of tenderness. The swelling then tends to diminish till the glands become smaller than before; but I have seen no case where the glands were so reduced in size as to indicate the hope that they would thus be cured without the intervention of the surgeon to remove the presumably necrotic tissue. In a case treated, since my return, in the Royal Sick Children's Hospital here, the primary increase was well marked, and the subsequent decrease was very striking. In this case there was much free exudation from the affected areas through the numerous sinuses which existed; these, prior to injection, had scarcely been discharging at all.

In articular conditions the process is necessarily much slower, and in the comparatively short time available for observation it has been impossible to follow those far. In a large proportion of cases, in addition to the general reaction, a definite local reaction was traceable, manifested, it might be, by increased swelling or tenderness—sometimes both—sometimes by abnormal fixation, to be followed, in the three or four cases which appeared to me to be making progress, by loss of tenderness, by increased power of voluntary movement and less discomfort when free passive movement was attempted. Dr. Levy showed one or two cases of tubercular arthritis in which he noted evident improvement. In Professor von Bergmann's clinic, during the ten days I visited the wards, I could recognise definite improvement in those directions in one or two cases. As a result of injections of several cases of glandular and articular tuberculosis other situations were sometimes indicated as probably seats of tubercular action, from the appearance of more or less characteristic local reactions.

With regard to internal conditions, I have had an opportunity of studying a very large number of cases of phthisis pulmonalis, phthisis laryngea, pleurisy, empyema, tubercular diarrhoea, etc.

In most instances the cases are being observed with great care. The state of the patient is carefully noted for a day before the inoculation, and a thorough examination of his system made, so as to include as much as possible every tubercular manifestation. The sputum is examined with care and frequently reported on. The temperature, pulse, and respiration are noted for twenty-four hours prior to injection.

In Professor Gerhardt's wards (where, through the kindness of the physicians, I had excellent opportunities for observation) the presence of the tubercle bacillus in the sputum was taken as the test of the case being presumably one of tubercular phthisis. Cases were included for observation only where the condition was reasonably early, and where, in other words, it might fairly be supposed that the tubercle bacillus was not abetted in its work of destruction by other organisms, which have been described in connection with late processes.

Special clerks, or other trained assistants, are told off to make note of every change, and the pulse, temperature, and respiration are noted every hour, or once in three hours (in some cases). Very much the same method is being followed in the Edinburgh Royal Infirmary, where the resident medical officers have been most assiduous.

Speaking generally for these internal conditions—and particularly for phthisis—the treatment is commenced with 0.001 gramme in the adult (or, in some strong, healthy subjects, 0.002 gramme).

In almost every case where there was reasonable ground for diagnosing phthisis the characteristic general reaction occurred. This differed in no respect from that witnessed in connection with the local processes, except that the severer symptoms, such as rigors, were generally absent when the dosage was kept small, along with the changes in pulse, temperature, and respiration already noted; but headache, lassitude, and occasionally vomiting occurred.

The local reaction, which occurs in from six to twelve hours, manifests itself by increased respiration (often more marked than in the ordinary general reaction), pointing to change in the lung, by a subjective feeling of dyspnoea, often by a peculiar sense of oppression and tension, as if the lungs were too big (as one patient expressed it), by cough, or increase of cough if already present, by increase of expectoration, which usually became more frothy and fluid (in some cases more uniformly purulent). In six cases hæmoptysis followed, but only in one case to any important extent—and in a patient liable to it. But, more interesting still is the change which occurs to physical examination. In a fair proportion of cases the percussion area of dulness was found to be increased, and in a considerable number the auscultatory phenomena of crepitations became more numerous. In some five or six cases I examined, where practically no dulness could be determined prior to inoculation, it became evident after, as did also crepitations not previously audible.

With regard to final results in these cases, especially in phthisis, it is premature to say much. In very advanced cases, of which I had the opportunity of studying about a dozen, I cannot say that I was satisfied of any definite improvement. The *post-mortem* results of the two or three fatal cases, so far as they have been communicated, point, however, to a local influence having been exerted on the affected organs.

In less advanced cases, but still cases where, prior to the special treatment, physical examination revealed considerable areas of

percussion and abundant crepitations, and when the patient suffered from loss of flesh, hæmoptysis, night sweats, and anorexia, the report must be more hopeful.

In a considerable proportion of these I think we may safely admit that very definite amelioration can be effected. I observed a number of cases where night sweats had disappeared, where the cough was practically gone, where there was a diminution or cessation of expectoration, and where the patient's subjective condition was better, and a few where there was a gain of several pounds in weight. In very few cases was I able to trace important improvement in the physical signs; but the time was too short for this, and no case has, so far as I was able to learn, been released from treatment as cured. Still I think, pending further observation, we are bound to fall back on the authority of Koch, who states categorically that "within four to six weeks patients under treatment in the first stage of phthisis were all freed from every symptom of disease, and might be pronounced cured."

With regard to the change in the tubercle bacilli, very varying statements are made by different observers. Professor Fränzel states that in a considerable number of cases the bacilli disappeared altogether, and that even when they did not they became smaller and thinner, as if they were starved; sometimes they became altered in form, becoming biscuit-like; sometimes they were broken up or apparently partially disintegrated.

To summarise a little, then, there can be no question that the fluid, whatever its nature, has a most defined specific action on the tubercular process, wherever situated. It seems to have the power, when introduced into the circulation, of finding its way straight to the seat of tubercular disease, however obscure or ill-defined this may be to external examination. Many of the cases I have already cited illustrate this well—the appearance of fresh lupus patches, the indications of pain or swelling of joints which had not previously been detected, and the reddening of old tubercular scars. Most striking in this connection are some dozen cases where I had the opportunity of examining the larynx after one or two injections. Here, as I was informed by the physicians of the wards, no change had been detected prior to inoculation (most of the cases were phthisis laryngea). Subsequent to inoculation, there certainly was a distinct indication of disease. In two or three this was shown by swelling of the aryteno-epiglottidian folds; in three cases by excoriation and even ulceration of the laryngeal surfaces, and, in one instance, by ulceration of one of the upper rings of the trachea.

Again, in three cases (lupus, supposed pernicious anæmia, and a doubtful apical catarrh) physical signs were detected after injection, and an abundant expectoration, not present before, was established.

In two cases, ultimately determined to be cancerous—one of the larynx and one of the face—the final conclusion was reached in virtue of the definite reaction manifested. This is also illustrated by some three cases of pleurisy, two with effusion, where injection produced a most definite reaction, proving the presence of a tubercular process somewhere, and presumably affording corroboration to the view that a large proportion of these pleural processes are tubercular. In one case under treatment in the Royal Infirmary no definite reaction, general or local, has occurred after four injections, although the dose has been increased to 0.01 gramme.

To what I have said of its curative value I do not propose to add anything. This has been sufficiently illustrated in the less severe and slighter forms. As to the limits of this and its duration, the time is yet too short to enable us to speak. But it is only fair to admit that up to a certain point this has been established.

The facts which have been made public regarding the effects of treatment in late cases of phthisis are discouraging, undoubtedly, but they form the strongest argument, as Koch has pointed out, for far more conscientious care in the early diagnosis of such cases, and for the use of all the means which later research has suggested, such as the careful examination of the sputum for the tubercle bacillus.

The cases which, through the kindness of a number of the physicians and surgeons of the Royal Infirmary and Royal Hospital for Sick Children, I have been enabled to place under treatment, and to which reference has here and there been made above, include eight cases of phthisis, three of pleurisy, two of lupus, two of tubercular adenitis, one of tubercular affection of the knee-joint, one of cardiac disease with obscure lung complication, and one of probable genito-urinary tuberculosis. Without entering

into further details, it may be well to say that all we have seen corroborates generally the statement made in Koch's original statement.

CASES OF PHTHISIS TREATED BY KOCH'S REMEDY.

REPORTED BY WILLIAM HUNTER, M.D., M.R.C.P.

(From the Augusta Hospital, Berlin.)

I GIVE here the notes, with temperature charts, of three cases of early phthisis which have recently been admitted into the Augusta Hospital, Berlin, under the charge of Professor Ewald. There are at present over fifty cases of phthisis and lung affections under treatment in this hospital, and through the special kindness of Professor Ewald, to whom I desire to express my very grateful thanks, I have been enabled to study the effects of Koch's new treatment as carried out under conditions—hygienic and dietetic—more than usually favourable to success.

Early Cases of Phthisis.—I have selected these three cases as being specially suitable for further observation; and I propose to record from week to week their further progress, with special reference to the following points: 1, the general condition of the patient as regards appetite, sleep, etc.; 2, body weight; 3, night sweats; 4, cough; 5, character and quantity of sputum; and 6, more especially the physical condition of the lungs before and after treatment.

CASE 1.—K. M., merchant, aged 31, was admitted on November 12th, 1890. The family history was good; both parents were healthy, and the sisters also were healthy. He had had measles, scarlet fever, and diphtheria while a boy. At the age of 23 he had inflammation of the lungs. His present illness began three

years ago with cough and expectoration, and since then he had suffered from night sweats and had lost flesh. When admitted he was a somewhat thin and poorly developed man, of a pale and sallow complexion. His general health was good; his appetite fair; the alimentary, urinary, circulatory, and nervous systems presented nothing abnormal. Cough was troublesome, expectoration fairly abundant, muco-purulent in character. There was considerable dullness over the right apex in front as far as the second rib, slight dullness also above the left clavicle. Posteriorly there was dullness in both supraspinous fossæ. The breathing over the