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Contributors

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ON
KOCH'S NEW TREATMENT
OF
TUBERCULOSIS.

BY

R. W. PHILIP, M.A., M.D., F.R.C.P.ED., F.R.S.E.,

ASSISTANT PHYSICIAN TO THE ROYAL INFIRMARY, EDINBURGH;
PHYSICIAN TO THE VICTORIA DISPENSARY FOR CONSUMPTION AND DISEASES OF
THE CHEST; LECTURER ON THE PRACTICE OF MEDICINE,
EDINBURGH SCHOOL OF MEDICINE.

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Two of the papers which follow were contributed to the December issue of the "Edinburgh Medical Journal." The last formed a communication to the Medico-Chirurgical Society of Edinburgh, on December 3rd. At the request of several friends, they have been reprinted together for convenience of reference.

R. W. P.

4 MELVILLE CRESCENT,
EDINBURGH, CHRISTMAS, 1890.

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I.

DR. KOCH'S COMMUNICATION— A RÉSUMÉ.

KOCH'S great secret has been disclosed in outline. Though there is abundant room for theorising in many directions, the sketch is clear and strong, and lets much of the completed picture be anticipated. In a delightfully simple style, one of the grandest therapeutic advances of the century is unfolded in an article entitled, "A Further Communication on a Remedy for Tuberculosis," which appeared in the *Deutsche Medicinische Wochenschrift* of November 13, and which will live in the archives of the nineteenth century, along with the papers of Edward Jenner, James Simpson, Louis Pasteur, and Joseph Lister, when most of the ephemeral productions of the day have ceased to be remembered.

It would be obviously foolish to attempt to examine the principles, still less to offer any criticism of the details of a system which has been the evolution of months and years of close study and patient investigation. But it may be of advantage to summarise and emphasise some of the salient points—both positive and negative—of so vastly important a statement.

The operative part of the method is extremely

simple, and does not differ materially from that of hypodermic medication, the injection being made into the skin of the back, between the shoulder-blades, and of the lumbar region. Those sites were selected on account of the comparative absence of local reaction manifested.

Of the constitution of the fluid little is indicated. Physically it is described as a "brownish, transparent liquid," which for use is diluted with distilled water. The original fluid keeps well, but the diluted fluid is liable to decomposition, unless used at once. Physiologically it is possessed of very special characters. In the first place, it has a far more potent influence—not merely relatively, but absolutely — on man than on some of the smaller rodents. Taking bodily weight into account, the 1500th part of what has no appreciable effect on the guinea-pig produces a powerful effect on the healthy human subject. So small a quantity as the quarter of a cubic centimetre — 0·25 gramme — produced, within three or four hours (in Professor Koch's own person), symptoms of pain in the limbs, lassitude, cough, dyspnoea, and, later, shivering, nausea, and vomiting, with a rise of temperature to 39·5° C. (103·3° F.) At the end of twelve hours these symptoms abated, and gradually disappeared. When the dose is reduced to $\frac{1}{100}$ th of a cubic centimetre—0·01 gramme—the reaction on the part of the healthy human subject is reduced to a minimum.

But the apparent simplicity of the procedure ends here. For when the method is transferred to the subject of tubercular disease—in

any of its forms — different and absolutely unexpected results are witnessed. With the reduced dose* — the $\frac{1}{100}$ th of a cubic centimetre — there is manifested both a *general* and a *local* reaction.

The *general* reaction commences from four to five hours after the injection, and the symptoms are very similar to those described in connection with the larger dose — $\frac{1}{4}$ cubic centimetre — in the healthy subject. The patients appear to suffer little from the attack, which lasts from twelve to fifteen hours.

The *local* reaction shows itself *not at the point of injection, but where the tubercular focus exists*. This has been studied most easily in lupus. When the injection is made at the sites already mentioned, the diseased area — for example, the face — becomes the seat of violent action — swelling, congestion, followed by necrosis and crusting, and, finally, within days or weeks, by healthy cicatrisation. The *extent* of local reaction is *limited with exactness to the diseased area*. Similar changes have been traced, more or less definitely, in connection with tubercular bones and joints, and presumably, judged by results, in lung tuberculosis.

The explanation of this extraordinary “elective affinity” cannot be discussed till, on the one hand, the constitution of the fluid is known, and, on the other, a thorough examination of the local histological changes has been reported. It seems proved, however, that the remedy does not destroy the tubercle bacilli, but rather the affected tissue.

* For phthisical patients this dose must, as explained later, be further reduced.

It will be recognised, then, that a two-fold value may be predicated of the method—(a) diagnostic, (b) curative.

The *diagnostic* aspect is many-sided. It is shown that with a minimal dose the specific reaction which has been described occurs *in the tubercular subject only*. Patients suffering from other diseases — *e.g.*, syphilis — are as insusceptible as is the healthy subject. Hence a positive or negative result following on such a dose will prove or exclude tubercular disease. But, further, given a tubercular subject, it is shown that the dosage of the fluid may be rapidly increased, apparently not because the system becomes more tolerant—the change is too rapid for this—but, presumably, because with each injection the amount of tissue capable of reaction is diminished. When a point has been reached at which the reaction ceases to differ from that shown by the non-tubercular subject, the diagnosis may be given that the tuberculous tissues have been destroyed and a cure effected.

The *curative* value of the method seems clearly established in the more superficial and better localised forms of tuberculosis. Subjects of inveterate lupus have been restored to health, recent and slighter cases of glandular, bone, and joint tuberculosis have been cured, and severe cases improved. Patients suffering from pulmonary tuberculosis appear to be much more susceptible to the influence of the remedy, and the dosage requires, accordingly, to be relatively less at first, and to be graduated with more care. But it is affirmed 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. Patients, with cavities not yet too far advanced, improved considerably, and were almost cured." And even in advanced cases, where objective proof is more difficult, expectoration decreased, and the subjective condition improved. Concerning pulmonary phthisis—especially in the later stages—Professor Koch is guarded in statement throughout, indicating what must commend itself to the impartial observer, that it is still too early to speak of *lasting* cure. But, fairly enough, it is suggested, that even if *immunity* is not obtained—a possibility which is not excluded—the relapses which occur may be treated with an equal measure of success.

The results in pulmonary conditions are pregnant with suggestion. On the one hand, they increase enormously the responsibility laid on medical practitioners to *diagnose phthisis in its initial stages*. Advantage must be taken of all available means, including, it may be—if further experience confirm the validity of the test—Koch's diagnostic injection. In particular, no physician can afford to look lightly on the objective proof afforded by a thorough examination of the sputum, whose significance has hitherto in some quarters been disparaged. He who omits such recognised helps must be regarded as "guilty of the most serious neglect of his patient, whose life may depend on the diagnosis and the immediate application of the specific treatment."

Professor Koch makes it abundantly clear that the adoption of the principles and practice

which he advocates, in no sense implies an abrogation of other auxiliary means. On the contrary, his teaching recognises the necessity of conjoining the new with all thoroughly accredited methods of treatment, and it discloses an immense vista of possibilities of therapeutic advance along many lines, towards the consummation of which the physician and the surgeon will in future, more than ever, be called on to combine.

Whatever may be the final judgment on the practical outcome of this admirable production of brilliant conception and most painstaking intellectual effort and skill—and time alone can pronounce this—not even the coolest critic will grudge the pæan of praise and gratitude in which a groaning and travailing creation now celebrates the latest triumph of the discoverer of the Tubercle Bacillus.

17th November 1890.

II.

FIRST REPORTS FROM BERLIN AND EARLY IMPRESSIONS.

Professor Koch's simple and masterly statement has been followed closely by several important communications of a more detailed nature from those whose experience in the application of the new method entitles them to speak with full authority. The *Deutsche Medicinische Wochenschrift* of November 20th contains four such papers from representatives of different departments of medicine. It will be my endeavour, in the limited time available before the publication of the December number of the *Edinburgh Medical Journal*, to supplement my brief *résumé* of Koch's original paper by an analysis of the results detailed in these, and a short statement of the impression which a visit to most of the clinics, where the work is being carried out, has made upon me.

Professor Fräntzel and Dr. Runkwitz give the results of their application of the specific in the wards of the former in twelve cases of phthisis pulmonum. The cases are divided into two groups:—I. Very advanced cases, numbering four, in all of which both lungs were gravely involved, and signs of serious implication of the system generally existed. II. Less advanced cases, numbering eight, in all of which the physical signs of phthisis were well marked, and the sputum contained tubercle bacilli. The conclusions of these observers,

after several weeks, are as follows :—Group I. The injection did not succeed in preventing the advance of the process in any one case, although three of the patients showed definite signs of reaction to the fluid by rise of temperature. *Post-mortem* examination in two cases proved that, while there was no evident tendency towards recovery, a definite local change had occurred. Group II. In every case improvement was noted. This consisted in a gain of weight, varying from about two to ten pounds (after from two to eight weeks' treatment, loss of more urgent symptoms, such as night sweating, hæmoptysis, and cough, a diminution in the amount of the expectoration, and a diminution or disappearance of the tubercle bacilli, with a corresponding betterment of the patient's subjective condition and appetite, and in some instances a distinct alteration in the physical signs. In addition to these, there was noticed a manifest effect on the tubercle bacilli themselves, even when they did not disappear from the expectoration. *Firstly*, the bacilli were observed to become smaller and thinner, so that they were with greater difficulty distinguishable; *secondly*, some bacilli assumed a distinct biscuit form; *thirdly*, others were found broken into two pieces; and, *fourthly*, when not actually broken in two, they were manifestly disintegrated into several fragments which remained fixed together like beads on a necklace.

From their results these observers are inclined to conclude that where there is manifest evidence of large vomicae, less can be predicted of the method than might be hoped

by the over sanguine. Regarding the *limits* of advancement, however, when the prognosis is to be regarded as less favourable under the system of Koch, the authors express some doubt, as the possibilities for observation have been too restricted. And they point out further that it will not do to conclude that so soon as a patient has ceased to react to the specific that he is thenceforth cured, as the authors have observed cases where clearly, after the specific had apparently ceased to cause reaction, an injection made after the lapse of some time induced a reaction, presumably from a process of auto-infection from some focus of the organism which had not been discharged by expectoration.

Professor Bergmann communicates the results of his experience in the surgical wards under his charge. The cases on which his statement rests are divided into four groups:—

I. Thirteen cases of tuberculosis of the skin and oral mucous membrane (including lupus).

II. Four cases of glandular tuberculosis.

III. Sixteen cases of tuberculosis of joints and bones.

IV. Four cases of laryngeal tuberculosis, and one or two of tuberculosis of other organs.

His results may be shortly summarised thus:—

GROUP I.—Those cases showed, after injection, the characteristic general and local reaction, which has already been described by Koch. In particular, the local manifestations were watched with care, and consisted in redness, especially well marked in the periphery of the affected area, and swelling, often very

considerable. Both the redness and swelling extended, in varying degree, in different cases beyond the affected area. After each repetition of the injection the local reaction became less evident. The original seat of the lupus gradually got covered over with crusts, sometimes of considerable thickness, which, where they were sufficiently advanced for removal or fell off, disclosed in a number of cases a perfectly smooth, delicate skin surface of red colour, like that of a fresh scar. In conclusion, Professor Bergmann cites a difficult case where he had been able to exclude, by means of a *diagnostic* injection, tuberculosis when other means of determining its nature had proved less certain.

GROUP II.—After the first injection the glands became more tender and swollen. As the treatment was continued the swelling diminished, till the glands became distinctly smaller than they had been prior to treatment.

GROUP III.—These included cases of hip-joint disease and of similar affections of the knee, vertebræ, and extremities. In all, there was distinct local reaction after injection. This was manifested by swelling, increase of tenderness, followed, in many cases where treatment had been of sufficiently long duration, by gradual improvement, shown by loss of local tenderness and of abnormal fixation, and increased power of movement without pain. Professor Bergmann concludes that for such cases the method affords an important aid to the surgical methods (which will still be necessary) in the direction of limiting the extent of the disease, and thus making operative inter-

ference possibly less extensive, and more certain in its results.

GROUP IV.—The injections had not been prosecuted sufficiently to admit of very definite statement. In one instance, however, after the second injection, the patient expectorated a mass which microscopic examination proved to consist of laryngeal tissue, with giant cells and tubercle bacilli.

Professor Bergmann draws particular attention to the *diagnostic* value of the method in connection with this group, and illustrates it by a case, which he had regarded as one of carcinoma of the left vocal cord, but where he thought it well to make the injection. The patient did not react to the maximal dose given to tubercular patients. He therefore believes that tuberculosis may be certainly excluded—a most important fact, when the difficulty of diagnosis of some laryngeal cases is remembered.

Professor Bergmann's general conclusion, then, from his extended experience, is that the *specific influence of the fluid on tubercular conditions is thoroughly well established*. To what extent it is curative, further experience must be allowed to decide.

The third report is from the pen of Dr. William Levy, who was one of the first to make trial of Koch's fluid on the living subject at the request of the latter. His observations date from the 22nd September, and in the earlier cases the dosage was fixed and regulated by Dr. Koch himself. The class of disease was similar to those discussed in Prof. Bergmann's statement, and the general history of the cases,

before and after the institution of the injections, is equally hopeful. Dr. Levy adds some interesting facts in relation to the functional disturbances which occurred in those cases where organs, such as the bladder, larynx, &c., were involved. In the case of the bladder, it is noted that after an injection at 10 A.M., there supervened, in the course of the afternoon, painful micturition, and towards evening, retention, the symptoms disappearing, however, in the course of the morning. Dr. Levy reports on one laryngeal case only, but it is satisfactory to learn that no appreciable dyspnoea is recorded. Two children, with tubercular affection of the knee, and a man of forty, with articular tuberculosis of the left hand, have been dismissed as cured, and a boy, with tuberculosis of the metatarsal bones, appears to be in a fair way to recovery. His lupus cases repeat the same story of success, in a greater or less degree of advancement, that has been already told. Dr. Levy indicates that the method cannot, of course, replace all surgical procedure. Rest and fixation of diseased parts, the removal of dead tissue, and the repair of lost portions will, as before, require direct surgical treatment, but the method permits, for the first time, of a rational hope of success,—a hope based on the sound principle of eradication from the system of the essential cause of the disease. The diagnostic value of the method in doubtful cases is also emphasised.

Drs. R. Köhler and Westphal report on twelve cases which have been under treatment in the extra ward of Dr. Bardeleben's clinic,—lupus, tuberculosis of bones and joints, &c.,

and scars, ulcers, and wounds. In four cases, where a tubercular origin was otherwise presumably excluded, injection of the fluid afforded definitely *negative* results. The injection was followed by less or more marked constitutional symptoms according to the dosage, but in *no* case was there any local reaction at the seat of lesion. On the other hand, in the eight presumably tubercular cases the local reaction was decided. This was again most marked in lupus, where in two hours after the injection a feeling of burning and tension appeared, followed in five hours by redness and swelling, associated with a distinct exudation, which gradually accumulated in yellow drops, and finally formed into crusts. For two days the exudation continued, and the crusts grew in thickness, the redness and swelling gradually diminishing. In five days the crusts began to break up and fall off. By the ninth day they could be easily picked off, leaving a smooth, pale red surface exposed. In the case of bone and joint tuberculosis, definitely marked local symptoms manifested themselves from the first, and, in some cases, soon after the injections were commenced, functional improvement was noted, apart from surgical interference. A detailed statement of the progress of these eight cases is appended.

Regarding the constitutional effects of the remedy, these observers conclude:—1. That tubercular subjects react much more strongly than non-tubercular. 2. That a more or less well-marked rigor generally occurs about six hours after injection, followed by a rise of temperature to 104° F. or more. 3. That the

temperature generally falls to the normal or below it within twenty-four hours. 4. That a repetition of the same dose gives rise to a less well-marked reaction. 5. That an increased dose is not by any means necessarily followed by a greater rise of temperature. 6. That apart from the rise of temperature, there is an increase of pulse rate, and, in many instances, there is induced a scarlatina like or similar rash, and in some an icteric tinge of the skin.

My own impressions may be described shortly, as much of what I should otherwise have stated has been included in the preceding *résumé*. I have had an opportunity of visiting a considerable number of the institutions and clinics where the method is on trial, and have to acknowledge gratefully the courtesy which has been extended to all medical visitors. The physicians and surgeons and their assistants have been most willing to show their patients and to discuss the procedure, so far as their experience entitled them.

Speaking generally, one recognises two schools of thought. There is the highly sanguine disciple, who has been less or more directly associated with the practice of the method from the first, and there is the calmer and, perhaps, more critical observer, who prefers to suspend judgment until for himself he sees the prints and thrusts his hand into the wound.

Up to a certain limit all are agreed. There can be no possible doubt that the fluid, whatever its nature, has a *distinctly specific action on tubercular processes of all kinds*. There is further unanimity in the feeling that the

method inaugurates a completely new departure in the treatment of tuberculosis, and, consequently, of all infectious diseases, and that the experimental and clinical results already obtained justify the belief that the method, which is the result of many years of most exact and patient investigation, possesses the permanency and potency of truth, however much the system may have to be elaborated.

As to the degree and kind of value to be predicated of the method, there seems divergence of opinion. Some enthusiasts have rashly exposed themselves to criticism by apparently sinking all other aspects of tubercular disease except that which has been established through Koch's earlier work. Thus, in some instances, I have seen patients with all the signs of very advanced phthisis allowed to stand for more than an hour in a crowded, ill-ventilated apartment, elbowed and jostled by the stronger or the curious, till, perhaps, half fainting, they have had to leave the room. Manifestly these are abuses which excitement and over-enthusiasm may explain, but cannot excuse. Very different from this reads the frank and prudent statement of Koch in his original paper: "In many cases I had the decided impression that the careful nursing bestowed on the patient had a considerable influence on the result of the treatment, and I am in favour of applying the remedy in proper sanatoria, as opposed to treatment at home and in the out-patient room."

The calmer scientific attitude is represented by some of the physicians and surgeons of the

larger hospitals, who have begun the method more or less recently. They recognise the fact that tuberculosis had been already proved to be curable, as shown by *post mortem* reports and clinical observation, and they are unwilling to lay aside successful measures of treatment actually practised in their wards. They have, therefore, arranged in some instances parallel cases, some treated with, and others without, the new remedy. The result of such comparison will be looked for with much interest.

Regarding its diagnostic value, different views have been expressed. From its specific action on tubercular tissues, the least that can be said is that it will afford important corroboration of diagnosis, even when this may appear to rest on definitely ascertained data. But more than that must be admitted. As will be seen from the reports, the diagnostic injection has been *the* one determining element in several instances. One case I have just seen in the wards of Professor Leyden illustrates the point further. A girl had been admitted and treated for what appeared to be idiopathic pleurisy, and convalescence was well established. A trial injection was made two days ago, and it was found that she reacted generally, and that over the affected pleural area she experienced pain and other symptoms traceable to a local reaction. Such a case is most suggestive of fresh avenues of work regarding the relation existing between tubercular phthisis and other local lesions, whose etiology is still matter of discussion.

The general impression conveyed to my mind

by a visit to the different wards is largely corroborative of the different reports referred to. We are entitled, in my opinion, to affirm that a hitherto inconceivable advance has been made in the treatment of tubercular conditions of all kinds, and that in lupus and in other more superficial affections, and in the earlier stages of phthisis, the method has been proved possessed of definitely curative power. Regarding more serious lesions and the more advanced stages of pulmonary disease, it is admitted by all that the time which has elapsed since the first injection was made—just two months ago—is too short to entitle one to predicate absolutely the limits of this curative efficacy.

The remarkable communications, of which I have given a digest, form an earnest of an immense mass of evidence which will soon be forthcoming when the collective results of Berlin investigation alone—now being conducted on a large scale—are given to the world.

BERLIN, *24th November* 1890.

III.

FURTHER IMPRESSIONS OF THE TREATMENT AT BERLIN, WITH EARLY NOTES OF CASES TREATED IN THE ROYAL INFIRMARY OF EDINBURGH.*

The publication by Dr. Koch on the 13th 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 suggested the following summary of the impressions produced by the 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 Indian sherry. Of its chemical constitution little can be said

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

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 1000. 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 condi-

tions, such as lupus, tubercular adenitis, articular tuberculosis, etc., the dose begins usually at 0·01 gramme for the adult,* and 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

* In delicate subjects and children this is correspondingly less.

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 103·3° 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 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 (p. 23). 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 diarrhœa was noted. In some dozen cases I saw a distinct exanthem—something between scarlatina, roseola syphilitica, and measles, sometimes 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. In some, the skin appeared to me unusually pale. In a few instances, epistaxis was noted.

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 somnolence, lasting many hours, it may be. In some instances, the somnolence occurred apart from other cerebral conditions.

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. The incrustation grows

* Some of my Edinburgh observations throw some doubt on this.

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 a pale red colour. In some cases where I saw it picked off, the sore presented the appearance of a granulating surface.

I have seen 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 is 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 this subject, 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 presumably necrotic tissue. In a case treated, since my return, in the Royal Hospital for Sick Children 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, &c.

In most instances, the cases are being observed with great care. The state of the patient is carefully noted for a day before the inocula-

tion, 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.

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 and other hospitals here, where the resident medical officers have been most assiduous.

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.

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). This dose is repeated daily, if there be no special reason to the contrary, until it ceases to induce evident reaction. It is then increased by 0.0005 or 0.001, or, it may be, by 0.002 gramme, the results of each increase being watched with care.

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 superficial processes, except that the severer symptoms, such as rigors, were generally absent, when the dosage was kept small. The changes in pulse, temperature, and respiration, have been already noted. Headache, lassitude, and vomiting, occasionally, 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 a 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 that in a patient liable to it. 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 dulness, and abundant crepitations, and where 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 few cases was I able to trace important improvement in the physical signs, though evident *change* occurred. The time was too short for this. 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 Fräntzel 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. These observations have been questioned by other physicians.

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 absence of reaction. This *diagnostic* value is also illustrated by some three cases of pleurisy (two with effusion), where injection produced a marked 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 of pleurisy treated 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 its limits and 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 re-

search 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, of the Royal Hospital for Sick Children, and of Leith Hospital, I have been enabled to place under treatment, and to which reference has been made, number 33, and include*—

Of Phthisis,	15 cases.
„ Pleurisy with Effusion,	3 „
„ Lupus,	10 „
„ Tubercular Adenitis,	2 „
„ „ Disease of Knee,	1 „
„ Heart Disease, with obscure lung complication,	1 „
„ Genito urinary tuberculosis (?),	1 „

Without entering into further details, it may be well, at this stage, to say, that all we have seen corroborates the statements made in Koch's original communication.

* Up to 22nd December 1890.



