A Lecture ON A SPECIFIC TREATMENT OF LEPROSY.

DELIVERED AT THE LONDON SCHOOL OF TROPICAL
MEDICINE.

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GENTLEMEN,—I am specially indebted to Sir Patrick Manson, Dr. Daniels, and Professor Sandwith for their courtesy in giving me the opportunity of addressing you regarding my researches in respect of leprosy. Notwithstanding the abundance of the available material, I shall be as concise as possible.

The researches made by me (during nine years in the course of my official work in Turkey), for the most part in collaboration with my assistant, Dr. Reschad Bey, commenced with attempts to grow the *lepra bacillus* in pure culture.

Despite many interesting facts then observed by us, we did not succeed in growing the *lepra bacillus* in the form in which it is seen in the leprous tissue; we isolated, however, from several severe cases of nodular leprosy a characteristic micro-organism which on account of its specific characters and habitat we termed *Streptothrix leproides*. The material from which the cultures were made was obtained by throwing back a flap of skin including a non-ulcerated recent leproma, and taking fragments of lepra tissue from the under surface of the leproma; every precaution against outside contamination was, of course, carefully observed. The tissue so obtained was placed in normal salt solution, and incubated at 37° C. for several weeks. The filaments of the *streptothrix* were now observed growing from the mass in great profusion.

I may here state that I am unable to say with certainty whether there are any, and if so, what, generic relations between this micro-organism and the genuine *lepra bacillus*; but I can positively assert that it is not a question of an accidental impurity. In order to ascertain whether there were any such relationship with the *lepra bacillus*, I ventured on one occasion to inject a small quantity of a living culture in a very severe case of leprosy. Irrespective of a slight induration at the place of injection no result was observed; the patient, however, obstinately maintained that the injection had had a beneficial effect on him, and he was not satisfied until I repeated the injections at weekly intervals. Under this extraordinary treatment the patient, whose disease was severe and accompanied by high fever, became completely free from fever, and his extensive leprous symptoms retrogressed so rapidly and in so remarkable a manner that after two months he considered himself to be thoroughly cured and left the hospital. Seeing that similar results were also obtained in other cases of leprosy, we naturally made it our task to discover the curative principle contained in the cultures. Extensive trials demonstrated that substances soluble in water and passing into the culture liquid, and also certain enzyme-like substances, could be excluded; hence it was only the culture mass which remained to be investigated.

We now proceeded by first cultivating large quantities of *streptothrix*, and by chemically separating them. The division of the chemical constituents of the cultures into albuminoid and lipoid substances was a matter of course. It was soon found that the active principle certainly could not belong to the albuminoid substances, but was contained in the fatty substances, that is, in the ether extract. Upon careful investigation the ether extract turned out to be a complicated mixture of greatly varying substances; and it was only after much trouble and after employing new methods that we succeeded in discovering a chemically well-defined substance which, on the strength of very numerous trials, made on man, could with certainty be regarded as the sole carrier of the active principle. Strange to say, this substance, called "nastin" by us, is a genuine neutral fat, that is, the glycerin-ester of a high-molecular fatty acid.

Under the microscope it is seen to be precipitated in beautiful starlike crystals from its solutions. It is strange to say that nastin is a neutral fat, for we are accustomed to look upon genuine neutral fats as chemically very inactive substances. We have, however, proved with certainty that all the by-products of nastin, such as the fatty acids or soaps, have completely lost their specific efficacy.

Now, by giving suitable doses of pure nastin by hypodermic injection, there ensued more or less intense reactive processes in the leprous tissue. These reactions consisted in inflammatory swelling and saturation, in pulplike softening, in true suppuration and necrosis of the leprous formations, to which these processes were exclusively confined, the normal parts of the tissue remaining unaffected.

There existed very great differences regarding the capacity for reaction of individual leprous patients. Whereas some of them responded to nastin injections by very violent reactions of long duration and dangerous to life, a small number apparently proved completely refractory; between these two extremes there were greatly varying grades of "reactivity." In many cases, however, in which changes of the leprous tissue took place, one was able by means of the microscope to observe a classical bacteriolysis of the *lepra bacilli*; so that in a preparation there is seen at first, besides well-preserved bacilli, the occurrence of granules which, if still containing some fat appear red, if deprived of fat, blue. Later, when the bacteriolysis is at its height, heaps of small red and blue granules only are seen. Still later, when the bacteriolysis is in the decreasing stage, there are only a few isolated minute granules and fragments of bacteria, all the rest being completely dissolved and destroyed. By microscopical examination it is easy to observe that the bacteriolysis is always heralded by the bacilli being deprived of fat—that is, when Ziehl's staining method is employed, by the loss of this specific staining property.

On the basis of these facts I had first deemed the consequence of nastin injections to be the formation of fat-splitting ferments, now attacking and splitting up the nastin-like fat contained in the *lepra bacillus*, and thus depriving the lepra excreta of its resisting power due to this very fat. Seeing, however, that experiments *in vitro* made by means of lipolytic ferments on tubercle bacilli gave no results at all, we again resorted to trials on man. Starting from the observed fact that nastin reaction always occurred with pronounced participation of leucocytes, I tried to produce artificial leucocytosis in a few patients who otherwise did not react to nastin at all. A good result was obtained by means of intravenous injections of sodium cinamate (the hetol of commerce), but leucocytosis by itself proved to be quite ineffective. It was only when at the height of leucocytosis a small quantity of nastin was injected that reactions ensued every time, but they were of so energetic and violent a nature that we had to discontinue with further trials.

These very remarkable observations induced us to inquire more closely into the chemistry of cinnamic acid and into what happens in the human and animal organism. Cinnamic acid, as well as similar aromatic substances, are excreted in the form of hippuric acid, which, as is well known, is a substance formed synthetically from glycocholic and benzoic acid. In dogs, and probably in other animals, the synthesis does not take place until the kidneys are reached—that is, immediately prior to excretion. Hence, it follows that cinnamic acid is transformed in the tissues into benzoic acid. This, however, is a simple process of oxidation, which can easily be carried out in the laboratory.

Experiments made by me with the final product of oxidation—the benzoic acid—gave no results at all. The idea presented itself, therefore, of contemplating the possibility of there being an intermediary product of oxidation, and such a product, indeed, does exist—namely, benzaldehyde.

At this stage we resumed experiments *in vitro*; previously, for the want of genuine *lepra bacilli*, they were made with tubercle bacilli. It had been found that it is extremely difficult, or hardly possible, by means of the usual agents for the extraction of fat, such as ether, chloroform, benzine, etc., even after extraction extending over weeks and months, to deprive tubercle bacilli of fat so com-

Fig. (a).

Fig. (b).

Fig. (c).

Fig. (d).

Fig. (e).

Fig. (f).

Case 1.—Figs. (a) and (b), condition before commencement of treatment. Fig. (c), condition of hands after treatment. Skiagram of hand (d) before, (e) during, and (f) after treatment. Contraction of the last phalanx of the little finger has been produced by a contracting cicatrix.

Fig. (a).

Fig. (c).

Fig. (b).

Fig. (d).

Case II.—Figs. (a) and (b), condition at an early stage of treatment, showing disappearance of leproma from left arm. Figs. (c) and (d), condition after treatment.

pletely that they lose their specific staining property to Ziehl's method. In benzaldehyde we first came across a substance which completely frees (in our sense) the tubercle bacilli from fat. To attain this end, heating, it is true, has to be resorted to. By heating to 100° C, the tubercle bacilli are completely deprived of fat within ten to twelve hours; at a higher temperature within about half an hour. In these circumstances we hoped that, on human beings, benzaldehyde would prove to be the sought-for substance for activating nastin. But it had not this effect.

The activation through benzaldehyde was neither more nor less intense than that produced by cinnamic acid. In face of these facts there was left only one possibility—it must be a question of the benzoyl radical at the very moment of separation. The next well-known substance possessed of the benzoyl radical in a readily separable form is benzoylchloride; and, indeed, it was soon found that benzoylchloride in the cold deprives tubercle bacilli of fat in about twenty minutes, and does so instantaneously and completely after slightly heating.

On the strength of these extensive experiments *in vitro*, and after satisfying myself by trials on animals that benzoylchloride is innocuous, I deemed myself justified in making trials on sufferers from leprosy. Very soon—in fact, immediately—it was seen that by combining nastin with benzoylchloride the former was activated to quite an unexpected extent, but much work was still required in order to ascertain the proper proportion of concentration between nastin and benzoylchloride, for not only the efficacy but also the possible danger of the method greatly depend on this purely quantitative proportion. For my trials on man I employed 2 per cent. benzoyl solutions, to which nastin was added in varying proportion. It now was found that in the event of nastin exceeding a certain amount and being present in excess, very pronounced reactive processes occurred in cases of tuberculous as well as in nerve leprosy. In the case of the latter there occurred particularly curious phenomena, which I will briefly refer to as they are of general interest. The employment of undiluted nastin had already formerly been observed to be frequently followed by apparently fresh symptoms developing in distinct connexion with the injection. With a highly-concentrated benzoyl-nastin solution I was able to produce such symptoms artificially with almost experimental certainty. In most instances it was a question of suddenly-appearing eruptions which reminded one greatly of burns of the second and third degree. Seeing that highly-concentrated benzoyl-nastin solutions give rise to purulent reaction in the case of tuberculous leprosy, I think I may draw the conclusion that the described eruptions are due to an inflammatory, probably leucocytic, reaction within a leprosy nerve centre. Such reaction transfers itself in the form of a change in the condition to the as yet preserved nerve filaments leading to the periphery, where it gives rise to the described purely trophic disorders.

I make mention of these observations because I think they throw some light on certain hitherto but little explained symptoms of anaesthetic leprosy. If, however, we use for injections such low-concentrated benzoyl-nastin solutions in which benzoylchloride is present in excess, the reaction phenomena remain completely absent after suitable doses; changes in the leprosy tissue become manifest only after a considerable time, but the therapeutic influence is not less favourable, and, withal, absolutely innocuous. Here also special interest attached to the observations made in cases of the purely nerve form. In the case of the same patients in whom by means of the strong solutions I was able to cause the above-described intense reactions the extensive anaesthesia retrogressed with surprising rapidity.

From the photograph it will be seen how severe some of those cases were. In the photographs and radiograms of the hand and foot of a patient of this category it can be seen that severe mutilations already existed. This patient had, moreover, anaesthesia in the arms and legs so deep-reaching that he had burnt his left arm by placing it on a heated stove. After a few injections the anaesthesia had disappeared, and the patient was again able to distinguish clearly between all kinds of sensation—for instance, between pointed and blunt objects, heat and cold, etc.

Having thus succeeded in gradually ascertaining the correct proportion in which to mix nastin and benzoylchloride, and the interesting fact that there is a definite relation in the solubility of nastin in benzoylchloride, the provisional character of the simple nastin-therapy of leprosy at first essayed was at once done away with.

The difference between then and now is so remarkable, and the new combined method is so clearly superior to the former simple nastin treatment, both as regards reliability and constancy of the therapeutic results and the exclusion of the dangers arising from nastin reactions, that I no longer hesitate in highly recommending the treatment in its present form for general therapeutic use in cases of leprosy.

Numerous trials having demonstrated that pure benzoylchloride solutions are quite ineffective specifically, we can only assume that benzoyl is the really active substance which acts direct on the lepra exciter; it requires, however, in order to get at the bacilli at all and not to be wasted in other directions, the guidance, so to say, of the otherwise thoroughly passive nastin, which charges itself in oily solution with benzoylchloride; it is not, however, a chemical union, but rather a state of simple solution; in this way benzoylchloride is protected from being prematurely and uselessly used up. The nastin is carried to the lepra bacilli, to which, owing to its near chemical and physical relation, it attaches itself, and then benzoyl can fully display its antibacterial action in the fat-removing sense. When deprived of fat the lepra bacilli seem to be doomed; the human organism then effects with comparative ease the further dissolution and ultimately the complete destruction of the bacteria nuclei.

The conclusions drawn by me from my experience hitherto are summed up in the short sentence: Benzoyl-nastin is an agent which directly acts on lepra bacilli. This sentence expresses the advantages and the progress affected by our method of treatment of leprosy as compared with other therapeutic endeavours. On the other hand, it clearly points out the limitations of the method.

Let us just imagine for a moment how a chronic infectious disease, such as leprosy, arises. In the first place, there is the specific exciter, without which the disease, of course, is unimaginable; there is besides, however, the human organism, which actively reacts on the invading parasites and which admits of the originating of the real pathological formations, and supplies the anatomical substratum for what we perceive as visible symptoms of disease. It does not, however, always follow that in every case the symptoms disappear upon the destruction of the parasites. The coincidence of these two phenomena depends on many factors which have reference to characteristics and structure, size and resistance, seat and conditions of circulation of the pathological formations. The more transient and delicate these formations are, the more easily they are accessible to the blood and the lymph stream, the better are the prospects of doing away with the symptoms of the disease simultaneously with the exciter.

When entertaining such considerations, one will not wonder at the fact that even in the case of the nastin-therapy of leprosy, notwithstanding its specifically anti-leprosy character, there is perceptible occasionally a divergency between the influence exerted on the exciter of the disease and the effect on the morbid products; and I must draw attention to these points in order to forestall conceptions, mistaken in principle, concerning the capabilities of the method.

There are, indeed, leprosy nodules, even in comparatively fresh cases, which respond not at all or only slightly to the injections; but there are also leprosy formations (besides true forms of exanthema, also more solid, even massy infiltrations, some of them of large extent) which are acted upon and done away with by nastin not less promptly than, say, syphilitic eruptions are by mercury. Between these two extremes there are many graduations. Rapid visible results should not lead to overrating the new method of treatment and its natural limitations, nor should occasional absence of expected changes and retrogressions of leprosy symptoms lead to underrating the method. With patience and fairly clever individualizing one will be able—excepting, of course, in the most severe, hopeless cases—generally to effect at least the arrest of the leprosy process; frequently, however, far better results will be obtained. Such is my decided

opinion, formed on the strength of clinical observations and experience extending over a period of more than four years.

In order to give an idea of the therapeutic results obtainable in the case of leprosy patients solely by means of the benzoyl-nastin method, a few photographs are reproduced. In Turkey I had under treatment altogether forty patients for at least several months; I was able, however, to observe some patients for a considerably longer period, up to several years.

The photographs of Case I show the conditions in a severe case of nodular leprosy, with the extensive, partly ulcerated leproma of the face, the arms, and the hands; with tumours of the lymphatic glands on both sides of the throat. The patient, who at that time already suffered from extensive leprosy of the tongue, the pharynx, and larynx, and of both the testicles, was a very unruly individual, who after a short stay escaped from the hospital at night. After a few months he returned with immensely aggravated leprosy of the mucous membrane and severe attacks of suffocation owing to leprosy of the larynx, necessitating immediate tracheotomy. In the course of treatment, continued for more than twelve months, the patient got rid of the leprosy of the mucous membrane, the tracheal tube could be removed, and he now speaks in a clear voice.

The skiagrams show multiple osteo-leproma of the hands in this case prior to, during, and after treatment. It can be seen that the parts of the bone previously affected, partly greatly distended, partly even completely destroyed, gradually consolidated and ultimately presented again a normal structure of bone.

The result obtained by the treatment regarding the leproma of the skin is shown by the photograph of the hands, where, instead of leproma and ulcers there are left only flat cicatrices.

The photographs of Case II show nodular leprosy with specially large leproma. The first photographs—(a) and (b)—were taken during the treatment, and besides the large fungiform prominent nodules, very flat pigmented cicatrices, the residue of former tubera, may be seen on the left arm. Photographs (c) and (d) illustrate the therapeutic result in such a manner that no further description is required. The last picture shows the same result obtained by the therapy on the legs of the same patient, where the pigmented cicatrices still approximately show the size of the leproma at that place.

I would add, however, a few remarks regarding tuberculosis, whose exciters are so nearly related to the *lepra bacilli*.

The neutral fat of tubercle bacilli, which necessitated the employment of special methods for isolating it and which was produced by me a year and a half ago, is chemically and biologically very near to, perhaps even identical with, nastin. This neutral fat, which we will call tuberculo-nastin, acts in the case of sufferers from leprosy in the same way and with the same intensity as nastin does. And vice-versa the ordinary nastin, which is quite inactive as regards healthy men and animals, proves in respect of tuberculous individuals to be an extremely active substance which acts likewise in the sense of fat removal and of the granular decay of the tubercle bacilli, as has recently been recognized as regards the animal organism by Behring, who has seen and verified my cases of leprosy in Constantinople.

But the decisive and essential difference between leprosy and tuberculosis consists in this, that in the case of leprosy one's object is attained in general with the fat-removal and with the dissolution of the bacteria into granules, that is, the organism then is able to dispose of the remaining constituents of the nuclei of the comparatively but slightly toxic *lepra bacilli*. In the case of tuberculosis, however, it is the very deprivation of fat and the granular decay which renders the extremely poisonous endotoxins of the tubercle bacilli amenable to absorption, and for this reason much harm may be done by incautious injection of nastin. Nevertheless I think and trust, on the strength of numerous cases of the most varying forms of tuberculosis which have come under my treatment hitherto, that nastin—in greatly different concentrations than are used for leprosy, and, it may be, combined with antitoxic treatment—is destined to play a part in the therapy of tuberculosis also.

But observations to be made for many months, perhaps

for many years to come, will be needed before I can be in a position to recommend a tuberculosis-therapy which admits of being generally introduced. At the present stage of my studies in this highly controversial province I can but urgently caution against applying nastin in the concentration indicated for use in the treatment of leprosy, when dealing with patients suffering from tuberculosis. Sad experiences would be the result.

It is otherwise as regards leprosy; I am convinced that in leprosy the present benzoyl-nastin therapy is innocuous on the one hand, and hence may conscientiously be recommended for use to medical men; and that, on the other hand, it constitutes a real advance in the treatment of this terrible disease.*

ELECTROLYSIS IN TIC DOULOUREUX AND IN SPINAL SCLEROSIS.

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I SHOULD like to call the attention of the profession to the valuable results which can be obtained in tic douloureux, spinal sclerosis, and other conditions by ionic medication. The human body is an electrolyte, and electrical currents are only conveyed through it by the migration of ions (electrified particles of matter). A current through the body is a convection current analogous to the convection of heat. There is an actual transfer of material particles, each carrying one or more electrical charges on its back, from one electrode to the other in both directions. By this means drugs can be carried through the unbroken skin into the body, and exactly at the spot where the effect is desired. I will refer here only to the two conditions of tic douloureux and spinal sclerosis. Ionic treatment of tic douloureux has been recommended by Leduc and others. Leduc narrates several successful cases, but no previous reference to the ionic treatment of sclerosis is known to me.

Six cases of tic douloureux have recently been under treatment by me. In each of these great relief or a cure—whether permanent or not it is too early to state—has been obtained.

CASE I.

R. M., aged 58, recommended by Dr. Boyd, had suffered from tic douloureux for five months, the pain was stabbing and worst at night, but never entirely away. The patient was unable to sleep and in and out of bed all night, had difficulty in opening jaw, and was becoming exhausted; many remedies had been tried unavailingly. The first application relieved him for twenty-four hours; the second application three days later had a similar effect; after five applications the patient expressed himself as being greatly benefited, he was able to take food and to sleep, and the attacks had almost ceased.

CASE II.

A. B., recommended by Dr. Ronaldson; tic douloureux had followed herpes; the attacks were severe, keeping the patient awake at night. Four applications sufficed to remove the pain, but the patient suffered from nausea and giddiness afterwards; during the applications she was inclined to sleep. Each séance was followed by freedom from pain.

CASE III.

A patient of Mr. Cotterill, aged 73; she had suffered from tic douloureux for nine years. The first application gave her, in her own words, the first good night she had had without an opiate for weeks. Three or four séances greatly relieved her, but when the treatment was intermitted the pain had a tendency to recur; a renewal of the applications always led to improvement, and after a dozen applications she returned home greatly benefited.

CASE IV.

A patient, aged 34, recommended by Dr. Frost, complained of shooting pains in the side of the face and back of the neck. In this case the current was passed from the one affected area to the other by means of large electrodes placed over these areas. The result was satisfactory; when the patient returned some days afterwards, she said that she had had scarcely any pain since the treatment.

* The benzoyl-nastin solution is put up in ampoules containing each from 0.0005 to 0.002 nastin in sterilized olive oil. One such dose is injected hypodermically once a week. No reaction is observed with the smaller doses, but with the larger reaction occasionally takes place. It is not desirable to induce a marked reaction. In favourable cases, after some weeks or months the lesions gradually disappear. Kalle and Co., Biebrich am Rhein, have undertaken to prepare the material in a form ready for use.