An Address ON THE SPECIFIC ACTION OF DRUGS IN TUBERCULOSIS.*

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It is now well recognized that a patient suffering from tuberculosis who is placed under the charge of a doctor will, for a time at least, improve in health no matter what drugs, vaccines, or specialty of treatment may be employed. The beneficial result is due in this, as in other diseases, to efficient nursing, to the regulation of food, exercise, and sleep, and to light and fresh air. If only this effect were clearly recognized the number of "treatments" in vogue for this common disease might be diminished. The enthusiastic physician sometimes begins the new treatment so soon as the patient enters his wards, and he is apt to put down the wonderful effects which may follow to the new drug, a view which unfortunately he neglects to rectify when the patient dies. General hygienic measures are of primary importance in treatment, and it is not until all the beneficial effects, which we know will ensue from these alone, have been exhausted that we have any right to ascribe an effect, beneficial or otherwise, to a special treatment.

Drugs are employed in tuberculosis either with the object of attacking and preventing the growth of the tubercle bacillus or other organisms with which the disease may be associated, or of neutralizing poisonous toxins, or of removing or relieving symptoms. It is to the first group that I am directing your attention to-day.

The ideal for which we search is an internal antiseptic, something which will prevent the growth of the tubercle bacillus without injuring the host, and this principle of internal antiseptics has now come to be termed "chemotherapy."

COAL-TAR DERIVATIVES.

The ordinary common antiseptics like phenol and the coal-tar derivatives (cresol, guaiacol)—mercury perchloride and formalin, for example—act in the same way on almost all micro-organisms; their antiseptic action is greatly diminished by admixture with serum, and when injected into the animal body they destroy the animal before they destroy the parasites. Innumerable attempts have been made to synthesize more active antiseptics, and two recent products of the laboratory I will mention. By brominating cresol a tetrabromcresol is obtained, which is 250 times more active than phenol and only half as toxic; by brominating naphthol tribromnaphthol is formed, which prevents the growth of staphylococci in dilutions of 1 in 250,000. Nevertheless, as internal antiseptics they are useless: they affect body tissues before parasites, and much of their antiseptic action is destroyed by tissue proteins.

If these coal-tar derivatives (cinnamic acid, creosote, guaiacol, and the rest) exert a beneficial action on tuberculous patients, the explanation is not that they influence directly the tubercle bacillus. The same is, of course, true of formic aldehyde, at one time much in vogue as a vapour for inhalation by phthisical patients. Occasionally also it was injected intravenously, and not infrequently produced albuminuria, haematuria, and even coma. Formic aldehyde, of course, in the body at once combines with proteins and loses all antiseptic action.

ESSENTIAL OILS.

Essential oils have been the basis of many systems of "cure"; thus the oil of cinnamon and oil of garlic treatments have each had its day; it were idle to describe them in detail, as it is universally recognized that, like other specifics, they fail in the hands of the sceptical physician. Fischer made numerous experiments on animals and showed, for example, that menthol eucalyptol injections into tuberculous rabbits in no way altered the course of the disease. *In vitro* such antiseptics as thymol and the cresols inhibit the growth of virulent human tubercle bacilli in strengths of 1 in 10,000, and these are the most active members of the group. Guaiacol and cresote only inhibit in strengths of 1 in 1,000, so that as bactericidal agents they are valueless.

CALCIUM.

I will mention here two or three other substances which have been alleged to exert specific effects in tuberculosis, although not by direct destruction of the tubercle bacillus. Many have written on the beneficent action of calcium: thus Maendl treated 250 patients with intravenous injections of 5 c.cm. 10 per cent. calcium chloride every day or second day. The injections were given in alternate weeks, and each patient received twenty injections. All the symptoms were influenced favourably. Calcium deficiency is a well known condition of many disease, including tuberculosis, and calcium injections may influence favourably the condition by limiting inflammatory exudation, but they do not influence the cause of the condition.

SILICA.

Silica is another of these specifics of recent date. Maver and Wells, in a review of the literature on silica therapy, come to the conclusion that the beneficial effects described are not established. They made some experiments with silica casein metaphosphate on tuberculous guinea-pigs, but found no increase in the duration of life or alteration in the tuberculous process.

ARSENIC AND MERCURY.

The employment of compounds of arsenic and mercury is particularly instructive because each new introduction has been described as being curative by one group of physicians and worthless by another. De Witt described certain mercury compounds which cause fibrosis and healing of tubercles in different organs in slowly progressing chronic tuberculosis of experimental origin. These effects were not seen in the control animals, however long they lived. Mercuri-bis-*p*-nitrophenol and mono-ethyl-*p*-nitraniline mercury acetate were the compounds he used. The injections produced no nephritis in any animal. Inhalation of arsenic has been described as effecting cures by Chavant. On the other hand, careful experiments made with the likely organic arsenic derivatives such as arsphenamine and its silver compounds show that they have no action on the pathogenicity of the tubercle bacillus and no favourable influence on the disease.

QUININE DERIVATIVES.

Chemotherapeutic agents have a specific selective action on certain tissues and bacteria, probably physical rather than chemical, and, unlike the group we have considered up to now, their disinfectant action is not retarded by admixture with serum, but, on the contrary, is increased. How selective these substances can be may be seen from one example. Atoxyl is a cure for syphilis like salvarsan, yet atoxyl is no longer used because it dissolves in the tissues of the eye and causes optic neuritis and atrophy, an effect which is not produced by either salvarsan or inorganic arsenic. After administering atoxyl to animals, arsenic is found in the humours of the eye, but no arsenic is present after administration of the other two substances.

Two groups of organic compounds are especially remarkable for their chemotherapeutic action on bacteria. Quinine is the methyl ether of cupreine, and it can be reduced by nascent hydrogen to form hydrocupreine. The following

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table shows the effect of two derivatives of hydrocupreine in arresting the growth of certain micro-organisms.

	Ethyl Hydrocupreine (Optoquin).	Iso-octyl Hydrocupreine (Vuz n).
Diphtheria	1 in 100,000	1 in 750,000
Pneumococcus	1 in 400,000	Negligible
Staphylococcus	1 in 500	1 in 16,000
Streptococcus	1 in 1,000	1 in 80,000

The action of optoquin on the pneumococcus and of vuzin on *B. diphtheriae* is absolutely specific; the higher and lower homologues do not exhibit this effect. Further, these drugs act in the animal body as well as in the test tube, and enough can be given by medicinal doses to animals and men to clear the blood from these micro-organisms.

ACRIDINE DERIVATIVES.

The second group of drugs which exert a marked action on bacteria are certain derivatives of acridine. Trypaflavine was used during the war for infected wounds; it acts better in the presence of protein, but is not sufficiently selective or specific on micro-organisms in the presence of body tissues to be of any real value; it is easily absorbed and causes oedema. Rivanol is a more recent derivative of acridine. Morgenroth cured streptococcal infections in mice by injections of rivanol under the skin. The injections, to be efficient, must be made soon after infection and in the neighbourhood of the inoculated zone; rivanol will not cure a blood infection. Still its discovery is a great advance over any substance previously available, and we can look forward with some confidence in the near future to the introduction of new derivatives which will destroy acute infective agents.

The chemotherapeutical substances which are known to act on bacteria are without value in tuberculosis. Thus flavine and its silver salts do not influence the tuberculous process in living animals, and the same is true of the quinine derivatives which have been prepared so far. The destruction of the tubercle bacillus presents two special difficulties: (1) in the fatty and protective envelope surrounding the bacillus, and (2) in the small blood supply to the tuberculous lesions.

CERIUM.

Success, however, has been claimed for several metallic compounds, and I shall confine my remarks to three of these. The first is with cerium salts. Frouin experimented with fifty rabbits and thirty guinea-pigs; they were inoculated with bovine tuberculosis and treated by injections of cerium sulphate. All the animals died, treated as well as controls, but the treated animals survived from two to five months longer than the controls, and in *post-mortem* examinations showed considerable growth of fibrous tissue in the tuberculous lesions. Grenet and Drouin tried the effects of cerium earths in chronic tuberculous affections in patients. They state that two facts have been established—that these metals reduce the fats of the tubercle bacillus in cultures, and that they produce a mononuclear leucocytosis. Their procedure is to inject intravenously 2 to 5 c.cm. of a 2 per cent. solution for twenty days; this is succeeded by a period of rest for fifteen or twenty days, followed by a second and third series of injections. The patients improved in every way. The bacilli disappeared from the sputum, or if present were modified. Thus three of four guinea-pigs were inoculated with the infected sputum of treated patients; the guinea-pigs became sick and lost weight for two weeks, but at the end of two months they were normal again. These observers think the treatment of value only in afebrile cases. Renon and Esnault and Brou have confirmed these results, and also agree that in febrile cases the treatment is unsatisfactory. If cerium salts, including its allies, exert any action on tuberculosis it cannot be by direct action on the bacilli, since these salts and their compounds have little more direct action in killing the tubercle bacillus than potash salts. According

to the figures given, the inhibitory action is about 1 to 5 parts in 1,000 to prevent growth. On the basis of this slight inhibitory effect in cultures—and, what is perhaps more important, the production of leucocytosis—a small number of cases of human tuberculosis have been treated with cerium salts by repeated intravenous injections, and the patients have improved; but there is no mention of control patients given the same general care, without the salts. The evidence so far presented, however, is of little real significance. The fact that cerium has still its devotees in France is perhaps of some importance.

COPPER.

Copper salts have had a great boom in the past, though they have, at least for the time, lapsed into oblivion. Luton, in 1894, in a monograph, first drew attention to copper as a specific in tuberculosis. Graf v. Linden and her colleagues in Germany produced a complex copper lecithin compound of secret composition; it was alleged to produce wonderful results in the treatment of patients. It is now more than twelve years since the introduction of this compound, and yet there is an alarming spread of tuberculosis in Germany, and since the war we hear little of the cure. Koga, in Japan, soon after v. Linden, produced cyanocuprol as a cure, but Koga's discovery has not settled the tuberculosis problem in Japan. The Japanese are very active in tuberculosis remedies; they have made many new compounds, sometimes of copper, sometimes gold, and sometimes other substances; but their tuberculosis does not diminish.

When the copper treatment commenced nearly all the reports were favourable to its use (Meissen, Strauss, etc.), but more extended investigations on animals made with the sulphate, oleate, albuminates, cyanocuprol and others have established the fact that so far as these salts are concerned the treatment, at all events on animals, is valueless. Schroeder, in particular, is definite that the copper treatment serves no useful purpose. Nevertheless, experiments with the putrefactive bacilli *Proteus vulgaris* and *Clostridium fetidum* show that copper salts are very strongly antiseptic; even when present to the extent of 1 in 2,000,000 a perceptible action is observed. Copper salts might be useful remedies in diseases characterized by increase of the number of putrefactive bacilli in the gastro-intestinal canal, particularly as they are not absorbed. They are also very active against the tubercle bacillus *in vitro*. Eggers showed that the influence of copper upon tuberculous tissues is strictly limited to a local effect; a deep and distant action is not obtained. On account of the increased susceptibility of the vascular nervous system around tuberculous tissues the action of the copper is greater in these than in normal tissues. He could not confirm von Lintgen. He states that true affinity of the copper for tubercle bacilli does not exist, nor could he find an affinity for tuberculous tissues; finally, the copper treatment of tuberculosis is not considered to be a specific therapy.

GOLD.

The last drug about which I propose to speak is the gold treatment. Koch showed that KAuCy₃ (1 in 1,000,000) prevented the growth of tubercle in cultures; the presence of blood serum interfered with the action and reduced the efficiency to 1 in 25,000. Gold chloride inhibits when in dilution of 1 in 2,000,000; and yet, in the careful studies of De Witt, as in the earlier observations of Koch, it exerts no favourable influence on tuberculosis in animals.

Without reviewing the various papers dealing with this subject, I will sum them up by saying that the results of administering gold salts in tuberculosis were not better than those given by copper, whether on cultures of the tubercle bacillus, on tuberculous animals, or on patients.

Aurocantan was next introduced; it is a cantharidin-ethylene diamino-aurocyanide, and was soon found to be too toxic for use. It was succeeded by a compound with a very promising composition, "krysolgan," introduced by Feldt. This compound prevents the growth of the tubercle

bacillus in cultures in 1 part in a million. Nevertheless, animal experiments with this substance are not very promising, though clinical results, as published in Feldt's monograph in 1923, are certainly both hopeful and inspiring.

KRYSOLOGAN (?)

The last of the gold cures is that recently introduced by Moellgaard.* It is a double thiosulphate of gold and sodium, $\text{Au}(\text{S}_2\text{O}_3)_2\text{Na}_2$, which, although a well recognized substance, he calls sanocrysin. Like its predecessors it retards growth of the tubercle bacillus in glycerinated bouillon in such strengths as 1 part in a million, but how serum added to the cultures affects its action I did not discover. Nevertheless, this is a very important point, since such chemotherapeutic substances as exert an undoubted action on bacteria invariably act better in the presence of the tissue fluids. Moellgaard assumes that his gold injections destroy the tubercle bacillus *in vivo*, and states that doses which are not poisonous in themselves kill the tuberculous animal by producing a tuberculin shock. This shock begins with albuminuria and sometimes haematuria; it is followed by toxic myocarditis and pulmonary oedema. Non-tuberculous animals do not exhibit this shock.

The evidence to prove this important point is nowhere clearly set out—that is, that the shock in tuberculous animals after an injection of sanocrysin is due to the destruction of tubercle bacillus and the setting free of endotoxins, which act as tuberculin acts on tuberculous animals. To combat this shock Moellgaard recommends a previous injection of antitoxic serum, after which his gold cure may be injected with impunity. It would be interesting to know whether other metallic poisons cause a like shock.

Moellgaard made many experiments on calves, rabbits, and other animals to test his sanocrysin, and the treated calves certainly did better than the controls, and some of them recovered. His procedure was as follows: He injected a number of animals on the same occasion; after some days the animal which seemed least affected was chosen as a control. Dr. A. S. Griffith thinks that this was wrong, since the calves may have been infected before they were used for experiment. The injection of the tubercle bacillus would cause those which had acquired some increase of resisting power as the result of a spontaneous infection to react violently for perhaps a week, while the really susceptible animals would remain unaffected; one of the latter would be selected as the control. It is true Moellgaard made tuberculin tests when the animals were three weeks old, but their weights show that they were much older when injected. The experiments of Dr. L. Cobbett at Stansted under the Royal Commission showed that, in spite of ideal conditions and constant care, it was impossible to exclude spontaneous infection.

Another feature of importance in these experiments is that the cultures used were attenuated. The doses necessary to kill were enormous and many control animals failed to die or contract severe disease. The attenuation of the bacilli makes recovery much easier and the large size of the dose intensifies the severity of the reaction to injection in an animal already infected.

So far as I am able to judge of the value of the recorded experiments, they are suggestive, but certainly not conclusive. Some of the krysolgan and copper experiments on animals have been equally suggestive, and with regard to the patients it is early to draw conclusions; it is the opinion of those best able to judge that clinical records of treated patients must be kept for years before the true value of a remedy for tuberculosis can be gauged.

Sanocrysin, then, is still on its trial.

* A paper by Professor Moellgaard on the theoretical basis of the sanocrysin treatment of tuberculosis was published in this JOURNAL on April 4th (p. 643).—Editor, BRITISH MEDICAL JOURNAL.

Humleian Lectures

ON

SOME FORMS OF VOMITING IN INFANCY.

DELIVERED BEFORE THE ROYAL COLLEGE OF PHYSICIANS OF LONDON, MARCH-APRIL, 1925,

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LECTURE II.—VOMITING DUE TO OBSTRUCTION FROM NEUROMUSCULAR INCO-ORDINATION.

Etiology.

I COME now to consider the etiology of the second form of obstruction, that which depends primarily upon neuromuscular inco-ordination. The beautiful experiments of Bayliss and Starling have made clear the method by which a bolus of food is moved along the intestinal lumen. Excitation by the bolus produces a twofold reaction in the muscular tube—contraction in the segment above accompanied by relaxation in the segment below. The bolus, urged forward by the contracting muscles into the area of relaxation, thus evokes a succession of peristaltic waves which hurry it along the bowel. These peristaltic movements persist in an isolated loop of gut separated from its central nervous connexions. Nevertheless, the intestine is possessed of a double nerve supply which has the power of augmenting or of inhibiting intestinal tonus and movement. The inhibiting fibres pass in the splanchnic nerves and peripheral stimulation produces cessation of movement and relaxation of tone. Stimulation of the vagus is less uniform in its effect, but most often after a short period of inhibition there follows a long phase of unusual activity of movement, and at times the gut may be so contracted as to obliterate its lumen.

Little is known of the localization of the cerebro-spinal centres of these two antagonistic sets of fibres. The centre for the inhibitory fibres is generally thought to lie in the spinal cord, in the upper dorsal and lower cervical regions. Yet Ott obtained inhibition by stimulating the optic thalami and cerebral peduncles. Budge and Valentin showed that intestinal movements could be excited and amplified by electrical stimulation of the corpora quadrigemina and corpora striata. Bochart in Vulpian's laboratory obtained movements of the intestines of dogs by stimulating certain parts of the motor cerebral cortex. Our knowledge of the paths by which the higher centres influence the intestinal movements remains, however, doubtful, fragmentary, and contradictory. That emotional states are habitually accompanied by changes in the amplitude and frequency of intestinal movements is everyday experience. Cannon found that motor activity in the stomach and intestines of his cats lessened when the animals became excited or angry. Barclay, in studying the gastric tone and movement in normal individuals, describes the striking alterations produced by an unexpected stimulus such as a loud sound.

In considering the etiology of this group of disorders in infancy, characterized by a temporary failure of the inhibitory apparatus of the bowel, I put forward the hypothesis that in development the inhibitory apparatus is apt to lag behind the motor and augmentary apparatus. That at this early age we have to deal with an organism in which the inhibitory activities of the splanchnic nerves are functionally weak is suggested by a variety of considerations. It is perhaps to be expected that the supreme function of inhibition shall be that which is last acquired. In the case of the skeletal musculature a similar functional retardation of inhibition is the rule. The newborn infant, before the myelination of the pyramidal tracts, is rigid and spastic in all its movements. Until the cortex awakens and assumes control the infant is in a state of what might be called physiological diplegia. Only gradually does the power develop to relax antagonistic groups of muscles and to permit precise and effective voluntary movement.