Address in Pathology,
ON
CHEMOTHERAPY.
DELIVERED BEFORE THE SEVENTEENTH INTERNATIONAL
CONGRESS OF MEDICINE.
BY
HIS EXCELLENCY WILHELMUS GERHARD HAY
PROFESSOR DR. PAUL EHRlich,
DIRECTOR OF THE ROYAL INSTITUTE FOR EXPERIMENTAL THERAPY,
FRANKFURT-ON-MAIN.

It must be a great pleasure and a special honour for all of us to meet here in person on British soil for a scientific purpose, in order to take part in the great work which will be of benefit to the whole world. Are we not here in a country that has produced two men who must be considered among the greatest men of all times— Jenner and Lord Lister? Like a star in the darkness of his age, Jenner's great achievement, which broke the power of such an awful plague as small-pox, still shines with peerless splendour. And on the occasion of the last Congress that was held here we gathered with wonderful admiration round the bed of the one, through his introduction of antisepsics brought about a revolution in surgery which stands alone in the history of the art of healing. Here in England the first example of a tropical disease, a model for all other institutes of this kind, was created under the direction of Sir Patrick Manson. Through Ross's excellent work, Laveran's discovery of the cause of malaria was so far advanced that entirely new lines were opened up for the hygiene struggle against tropical and sub-tropical diseases. Castellani's proof that a trypanosome causes sleeping sickness, the classic work by Bruce on illnesses caused through trypanosomes, the specific cause of kala-azar (Dum-dum sickness) as proved by Leishman, are all well known to us. The therapeutic influence of atoxyl in trypanosomiasis was first established in the Liverpool Tropical School by Thomas and Breinl, and quite recently Pflüger has brought forward tartar emetic as an effective weapon against protozoan diseases.

The life-work of Almroth Wright is also known to all of us—his work on ophthalmia, and on the prophylactic treatment of typhoid fever, carried out in so practical and excellent a manner. Even these names, to which I might add many others, show what a high and leading position England has taken and still holds in the fight against infections diseases. To prevent the spread of and to heal the many different less always been the highest aim of medical ambitions. But a systematic pursuit of this purpose has only been possible in recent times, as through the labours of all civilized nations we have got an insight into the nature of infections, the cause of diseases, the means by which they are transmitted. Through these methods it has been possible to infect animals artificially, and so to obtain material on which to test the drugs in a systematic and rational manner.

From the very first beginnings of therapeutic chemotherapy there has, indeed, been in existence, as all the remedies which we employ are chemicals; on the other hand, experimental knowledge, which only developed in modern times in a fruitful manner as a result of all this pioneer work. But here also it has been proved that the four most important factors are patience, skill, luck, and, last but not least, money.

Now, gentlemen, I may perhaps take the liberty of giving you an insight into the workshop of chemotherapeutic research. The whole area is governed by a simple—almost every natural—principle. If the law is true in chemistry that Corpora non agunt nisi liquida, then for chemotherapy the principle is true that Corpora non agunt nisi floscent. When applied for advices that in point this means that parasites are only killed by those materials to which they have a certain relationship, by means of which they are fixed by them. I call such substances, characteristic, fixed, or specific. But it is easy to add that there are evident exceptions to this law. Thus, for instance, we are acquainted with a small series of cases in which the apparent therapeutic results are obtained, although the allied substances in question do not possess parasite-destroying qualities. That is the case in the infiltration of the ailments which are caused by a kind of yeast (sporotrichosis). Here Block proved that the clinically highly therapeutic potassium iodide first of all dissolves the cells of the infiltration, whilst the parasites, as such, are not in the first instance attacked. But, in any case, it is safest and best for the development of chemotherapy not to think of exceptional work, but to start with such substances as produce the destruction of the parasites by fixation.

Now it has been assumed in different quarters that some of the more modern remedies are incorrectly regarded as parasitides, but in reality they are not such. Thus, for example, salvarsan or mercury salts are not intended to act directly on the parasites but indirectly, owing to the fact that they excite the organism to the formation of specific antibasides. This view is based mainly upon the fact that if one mixes the substances in question, such as, for instance, neo-salvarsan, with certain pathogenic agents—for example, spirochates—in test tubes, one cannot perceive any reduction in their mobility after observing them for hours together. From this fact, which was first discovered by Professor Huts, the conclusion has been drawn that the salvarsan or neo-salvarsan did not in any way influence the spirochates directly. Now it can very easily be shown that this conclusion is quite incorrect. If, for instance, following Castellani, one suspends the spirochates in a solution of mercuric nitrate and then fills up the mixture of serum which do not injure their vitality, and if one fills two small test tubes therewith and adds to one of the tubes a very small quantity of salvarsan or neo-salvarsan, and if one allows the other centred in the second to centrifugate; then one obtains in each tube a deposit of spirochates which can be examined with a microscope examination shows a decided degree of mobility. If, however, the spirochates obtained in this manner are injected into test mice, then one can very soon convince oneself that the spirochates no not infect the animal, whilst the mice vaccinated with the contents of the control tube promptly show signs of infection. This proves that salvarsan or neo-salvarsan, as the case may be, is absorbed by the spirochates, and must have damaged them, and that this trace of salvarsan which is so exceedingly minute that it can scarcely be weighed, was sufficient to prevent the multiplication of the parasites. That this can be very simply and easily intelligible experiment, therefore, the direct effect of salvarsan and neo-salvarsan on the spirochates, and thereby the principle of fixation, is absolutely obvious. As the spirochates, the parasites treated with salvarsan do not infect the animal, whilst the mice vaccinated with the contents of the control tube promptly show signs of infection. This proves that salvarsan or neo-salvarsan, as the case may be, is absorbed by the spirochates, and must have damaged them, and that this trace of salvarsan which is so exceedingly minute that it can scarcely be weighed, was sufficient to prevent the multiplication of the parasites. That this can be very simply and easily intelligible experiment, therefore, the direct effect of salvarsan and neo-salvarsan on the spirochates, and thereby the principle of fixation, is absolutely obvious. As the spirochates, the parasites treated with salvarsan do not infect the animal, whilst the mice vaccinated with the contents of the control tube promptly show signs of infection. This proves that salvarsan or neo-salvarsan, as the case may be, is absorbed by the spirochates, and must have damaged them, and that this trace of salvarsan which is so exceedingly minute that it can scarcely be weighed, was sufficient to prevent the multiplication of the parasites. That this can be very simply and easily intelligible experiment, therefore, the direct effect of salvarsan and neo-salvarsan on the spirochates, and thereby the principle of fixation, is absolutely obvious. As the spirochates, the parasites treated with salvarsan do not infect the animal, whilst the mice vaccinated with the contents of the control tube promptly show signs of infection. This proves that salvarsan or neo-salvarsan, as the case may be, is absorbed by the spirochates, and must have damaged them, and that this trace of salvarsan which is so exceedingly minute that it can scarcely be weighed, was sufficient to prevent the multiplication of the parasites. That this can be very simply and easily intelligible experiment, therefore, the direct effect of salvarsan and neo-salvarsan on the spirochates, and thereby the principle of fixation, is absolutely obvious. As the spirochates, the parasites treated with salvarsan do not infect the animal, whilst the mice vaccinated with the contents of the control tube promptly show signs of infection. This proves that salvarsan or neo-salvarsan, as the case may be, is absorbed by the spirochates, and must have damaged them, and that this trace of salvarsan which is so exceedingly minute that it can scarcely be weighed, was sufficient to prevent the multiplication of the parasites. That this can be very simply and easily intelligible experiment, therefore, the direct effect of salvarsan and neo-salvarsan on the spirochates, and thereby the principle of fixation, is absolutely obvious. As the spirochates, the parasites treated with salvarsan do not infect the animal, whilst the mice vaccinated with the contents of the control tube promptly show signs of infection. This proves that salvarsan or neo-salvarsan, as the case may be, is absorbed by the spirochates, and must have damaged them, and that this trace of salvarsan which is so exceedingly minute that it can scarcely be weighed, was sufficient to prevent the multiplication of the parasites. That this can be very simply and easily intelligible experiment, therefore, the direct effect of salvarsan and neo-salvarsan on the spirochates, and thereby the principle of fixation, is absolutely obvious. As the spirochates, the parasites treated with salvarsan do not infect the animal, whilst the mice vaccinated with the contents of the control tube promptly show signs of infection. This proves that salvarsan or neo-salvarsan, as the case may be, is absorbed by the spirochates, and must have damaged them, and that this trace of salvarsan which is so exceedingly minute that it can scarcely be weighed, was sufficient to prevent the multiplication of the parasites. That this can be very simply and easily intelligible experiment, therefore, the direct effect of salvarsan and neo-salvarsan on the spirochates, and thereby the principle of fixation, is absolutely obvious. As the spirochates, the parasites treated with salvarsan do not infect the animal, whilst the mice vaccinated with the contents of the control tube promptly show signs of infection.
When a race of trypanosomes has been rendered immune to fuchsin, then this race is immune to all the dyes of fuchsin and methyl violet, but is not immune to the toxic and antitoxic agents. In the same way, a race immune to arsenic compounds is only immune to such, but not to the two other classes. We see, therefore, that the immunity is of a specific nature, inasmuch as it is limited to the class of chemical substances.

It was just this specific character which indicated that it must be a question of purely chemical processes. Earlier studies relating to another subject—that is, those relating to toxic and antitoxic principles—led to the nature of these processes. In connexion with them, it had been shown that the destructive toxins developed their injurious action on the cell by the fact that they are absorbed by certain specific components of the cell—aide—on which I have characterized as "receptors," and that the antitoxic substances represent nothing else than the cell receptors, produced in excess under the influence of the toxins and thrown off.

For many reasons I had hesitated to transfer these views relating to receptors to chemical bodies at all, and in this connexion especially, the helpful investigation by Langley relating to the effects of alkaloids which caused my doubts to disappear and made the existence of chemical receptors seem probable to me. The result of my own observations made in connexion with the "drug-fast" strain of germs can be readily explained experimentally, owing to the fact that the growth of the chemoreceptors under the influence of drug-fastness substances is a peculiarity of their affinity for certain components connected with the remedy, which can only be regarded as purely chemical. This reduction in affinity explains in the simplest possible manner why continually increasing quantities of the substance are necessary for the destruction of a race of arsenic-fast trypanosomes, for example, for the smaller avidity can only be overcome by a corresponding increase of the arsenic compound, if the quantity necessary for the destruction of the parasites is to be finally fixed.

We therefore come to the conclusion that in the parasites are present different specific chemoreceptors, for instance, the arseno-receptor, which fixes the trivalent group of arsenic as such; and the aceto-receptor, which fixes to itself the acetic acid group, an acetate, or an orthoacidophenolderivative, which conditions the fixation of the salvarsan, and many others in addition. A complete exhaustive knowledge of all the different chemoreceptors of a certain definite parasite is in my opinion desirable and necessary to characterize as the therapeutic physiology of the parasite cell, and this is a sine qua non of any successful chemotherapeutic treatment. I should like to emphasize this fact that any observations indicating that certain chemoreceptors are due to different specific kinds of parasites, not to a single one. The knowledge of these is of special practical importance, because remedies which are adapted to these have a healing influence on a very large series of the most various parasitic agents. The larger the number of different chemoreceptors, therefore, which can be demonstrated, the greater is the possibility of a successful chemotherapeutic treatment.

Now if we seek for specific remedies, then the first condition is that they must possess a certain definite grouping, which is chemically allied to one of the chemoreceptors of the parasite. This is only a necessary condition, but in general it is not a sufficient one in itself. Hundreds of substances may fix themselves on a parasite, yet only a few are capable of bringing about its destruction.

In the therapeutically suitable substance, therefore, in addition to the fixing group, which brings about the fixation, there is usually described a lignifying group, another, which as such brings about the destruction, and is to be characterized as the "poisoning" or "toxophoric" group. This representation exactly corresponds to the view that we have long maintained with regard to the toxins, in which we distinguish the presence of a toxophoric group which conditions the cell fixation and also the formation of the antitoxins, and a toxophoric group which conditions the cell destruction. In the case of the highly complicated synthetic drugs the assumption will have to be made that the toxophoric group and the toxophoric group are not directly connected with one another, but are linked by a chemical molecule in the character of side-chains as separate groups. In this way we come naturally to this, that chemotherapeutically active substances build up a fixed pattern, in which the poison is compared to a poisoned arrow; the fixing group of the drug which anchors itself to the chemoreceptor of the parasite corresponds to the point of the arrow, the binding number is the poison group, and the compound is sprayed on the arrow's head. Corresponding to this scheme in the case of salvarsan (dioxymethylbenzonitrile), the benzol group would correspond to the shaft, the orthoacidophenolderivative to the point, and the trivalent arsenic group would correspond to the toxophoric group on the head of the arrow.

If we continue this comparison, then the substances which are used for poisoning the arrows are alkaloids and similar substances, which act injuriously on definite vital organs of the body; and we shall also have to assume that the toxophoric groups of the synthetic drugs poison the protoplasm of the bacterial cell, and this only appears to be possible when a chemical affinity exists between the toxophoric grouping and the constituents of the cell. It is observed, too, that the toxophoric group is common to all the compounds which contain arsenic in the pentavalent form, that is, in the fully saturated form, do not bring about any therapeutic action, but that only commences when the arsenic atom is saturated in the unsaturated arsenic compounds which contain arsenic in the pentavalent form, that is, in the fully saturated form, do not bring about any therapeutic action, but that only commences when the arsenic atom is saturated in the unsaturated arsenic compounds, for example, in the case of the saturated coccidial acid with the pantivalent arsenic, and its poisonous reduction product the coccidial with the trivalent arsenic, he came to the conclusion that the coccidial acid had lost the toxic action of the poison with the arrow, and at the same time had lost its effect on the organism. In later times many analogous cases pointing to the increase of malignancy have been known. The best known example is doubtless the highly toxic action of carbon monoxide as compared with the almost indifferent carbon dioxide.

Dyes act as bactericides only when present as dyes, but not when in the form of their colourless products which correspond to the saturated type. The fact is that all these unsaturated compounds contain unsatisfactory vitamins which render them capable of making addition compounds with other bodies.

If, therefore, we poison a spirochete with salvarsan, then there occur at once definite phenomena. First of all, the fixation of the orthoacidophenolderivative, which primarily fixes the salvarsan to the parasite. It is only in consequence of this fixation that, secondarily, the trivalent arsenic group can be reduced to the poison by inging into chemical combination with the arseno-receptor of the cell, and so of exerting its toxic effect. The avidity of the arseno-receptor may be so small that it can only reach if favouring factors, which from the chemical point of view must be regarded as stereochimical facilitation, come into action.

Examples of such stereochimical facilitations are frequently found in the chemistry of the ortho-condensation, for example. And so the haptochromic group of the arsenic molecule primarily brings the arsenic to the cell, and secondarily brings about its fixation of action.

Now, it is a feature of many uneducated peoples to smear their arrow-heads with not one kind of poison only, but with two or three totally different kinds, in order to be certain of killing their enemies. And so it also appeared advisable to imitate this otherwise not very praiseworthy procedure against the parasites, and to poison our synthetically poisoned arrows not singly but doubly, or even triply. For instance, in the compound containing trivalent arsenic (salvarsan, for example) to metals, and so in producing remedies which, used experimentally on animals, show an increased effect.

In the present remarks I have described the conditions which are necessary if a certain substance is to exert a parasitically destructive effect, and indeed must affect such, if it is to contain directly on the cell. But the case of the highly complicated synthetic drugs the assumption will have to be made that the haptochromic group and the toxophoric group are not directly connected with one another, but are linked by a chemical molecule in the character of side-chains as separate groups.
humber of substances which will destroy bacteria and allied agencies in aqueous solutions. But, of course, the problem is much more difficult when it is a question of internal infection or of the destruction of living parasites within the infected organism. If the problem of subcutaneous inoculations is not more difficult, then indeed it is easy to do so, owing to the present advancement of science. But the task becomes more difficult when the wound is filled up with pus and mingle; and when these materials are of such a delicate texture as to give a greater difficulty to the natural actions and processes, then the difficulty of the problem will be manifest without any further explanation. A matter of fact, it has proved that substances which are already highly diluted bring about a colossal bactericidal effect in three times the solutions are totally inactive in therapeutics properly so called. For it has turned out that, generally speaking, these disinfectants are more or less poisonous, or seriously injure the organism; they are therefore not only parasitotoxic but also organotoxic.

Now, it depends exclusively on the relationship between the parasitotoxic and organotoxic to determine whether a certain disinfectant can be used as a remedy. In Robert Koch's celebrated experiment, in which even the largest doses of a substance did not produce a trace of therapeutic effect on the acute infection, it is evident that the parasitotoxic effect was reduced to nil by the organotoxic effect. If the relationship of organotoxicity to parasitotoxicity is somewhat more favorable, then one may observe a peculiar phenomenon, consisting in the compensation of the infection being rendered worse to an extraordinary degree by the remedy, owing to the effect that the parasitotoxic increases to a much greater extent than is the case when no organotoxic agent is employed.

This phenomenon, discovered by Hata, is explained by the fact that the ratio of organotoxic effect to parasitotoxic effect is such that the whole of the poison is absorbed by the organism, but only a very small portion of it is innumerable quantity by the parasites. According to a fundamental biological principle, it is quite a common thing for a destructive and damaging substance to produce a beneficial effect in large quantities to bring about an increase in the vital functions when given in smaller doses. The only substances that can be considered therapeutic agents are those in which the ratio of organotoxic effect to parasitotoxic effect is a favorable one, and that can be readily ascended by experimental comparison of the results with the dose tolerates. The only substances that can be considered therapeutic agents are those of which a fraction of the dose tolerates is sufficient to bring about therapeutic effects.

Drug effect of the various medicines is of course to be attributed to the views of Langley and myself, to this, that in the most various cells of the body and its organs quite different chemioceptors, exactly in the same manner, are postulated for the parasites. Apart from the pharmacological effect of the various remedies, this chemical difference of the organs appears clearly in the method of vital colouring.

I will therefore only indicate a few examples—the in-vitro staining of the nerve trunks by methyl blue, the staining of the cell granules by neutral red, and the distribution of leucine in the so-called pyroll cells so call. And excellently investigated by Edwin Goldmann. The pathologic-anatomical findings point also to a chemical divergence on principle. When we see the striking effect of the introduction of paraphenyleneamine on the summit of the dose tolerates, we assume a black colouring; when we see that tinylazine in the case of all kinds of animals isolates and injures the renal pelvis and causes them to die; when we see that the introduction of cyanate, as Hata and Goldmann have done, causes in a certain pathologically anaesthetic regions in the hair of mice become colored, and the colouring matter becomes stored to the greatest degree in the dogs which act destrucively; the colouring material of the pyrins series in the case of mice brings about a general coloration, amounting to 50-60 per cent. of the body weight without injuring the kidney, a phenomenon that doubtless is only to be noted by the concentration of the vessels of the subcutaneous connective tissues; then all these phenomena can only be explained by the fact that at these particular substances only chemical unions of a specific nature must take place, and must be referred to the presence of certain definite chemioceptors.

Now, according to the above views, all these fixations are dependent on the haptophobic grouping of the drugs. It was therefore a matter of great interest to observe how phynmaysenic acids or metal arsenic compounds, the modern arsenic compounds, behave when various different parasitic groups are attached to it. In this connexion it has been found that when we introduce different fixation groups—e.g., chloramphenicol, the cyanide group, the arsenic acid group, the sulphuric acid group, the ammonia radical—we can manufacture from a single substance a series of combinations with toxic effects varying fifteen-hundred fold. The combination of which are:—the more free from poison—these are derivatives of sulphuric acid, such as the sulpho-phenamycetic acid and its salts—five less toxic than sodium chloride. On the other hand these substances are the smallest quantity of which brings about death. In this connexion we can see that, according to the nature of the substances, very different organs of the animal can be affected. Sometimes it is the intestinal tract, and the animals die of poison diarrhea; sometimes it is the liver, and the mice—a rare and noxious species, and die of severe alterations in the liver; sometimes the renal pelvis, the hair of mice becomes dissolved, and the animals die of severe anaemia. Frequently also the central nervous system becomes destroyed, and in the case of mice the ventricular nerve of the internal ear. The interference of which is produced in this way causes the mice constantly to turn in circles, just like the Japanese dancing mice. In the case of human beings the eye is the point of attack for numerous derivatives of phenamycetic acid. The cases of blindness which have been observed after the use of very large doses of avotox, aracetin, and other drugs, are due to analogous injuries.

From this it is evident that according to the selection of the group combined with the phynmaysenic acid, quite different organs will be affected. According to the above views this is only explained by the fact that the substances already previously stated, in the various organs specific chemioceptors which energetically attract certain fixation groups to combine with them as much as possible, is not attacked. This view also explains why we find it impossible to construct our poisoned arrows. We must attach to the phynmaysenic acid group, or, as the case may be, to the phenamycetic acid group, such an atomic group as is but directly related to the organ of the stick body, but on the other hand is chemically very closely allied to the receptors of the parasites.

I have explained above the chemioceptors possess a whole series of chemioceptors which are chemically different from one another. Now if we can succeed in discovering among them a group which has no analogoue in the organs of the body, this would be the possibility of constructing an ideal remedy by selection for a haptophobic group specially adjusted to the function of the parasitic agents.
by my respected friend Professor Dr. Hata, and later by Dr. Czeliź and Dr. Gonder, and Dr. Leopold. Salvarsan has proved to be the most efficient, the disobonomelarnobenzol dichlorhydrate of the formula:

\[ \text{HCl} \text{NHN} \text{O} \text{N} \text{HCl} \]

Here the orthoamidophenol group acts as the conducting and the aminogroup as the toxicophoric group.

The next step from the laboratory to practice—to the bed—is an extraordinarily difficult and dangerous one, a step which can only be taken with the greatest care. Its difficulty and danger are in the main based upon two factors:

1. On the fact that in the case of man there exist so-called idiosyncrasies, forms of supersensitiveness which do not occur in the case of animals. So, for instance, it is known that with a large number of thoroughly healthy persons the consumption of harmless articles of food, such as strawberries, crab, etc., brings about unpleasant eruptions, and almost half of the known remedies can induce such phenomena of supersensitiveness. It will not be a case of surprise, therefore, that such phenomena may occur in a particularly serious form. The most dangerous of the groups of substances which contain such powerfully acting radicals as arsenic and mercury, we have already referred above to the disturbances of vision and cases of blindness which have been produced by certain arsenic compounds.

Fortunately, it is proved that such primary supersensitiveness in the case of salvarsan is one of the very rarest phenomena, and that it was perhaps due to a unique combination of circumstances, sources of error of a hidden nature, which in many cases has led to the mistaken idea that supersensitiveness existed. In this place we must first of all mention the studies of Mosdach and Fitts, and of Leete and Penfold, who have brought forward the very important proof that the destroyed bodies of bacteria may occur in sterilized water and are capable of bringing about a series of serious and unpleasant phenomena such as fever, vomiting, diarrhoea, etc. And even in the case of a pure and unexceptionable water technical mistakes in the manufacture of the salvarsan solutions may bring about an injury; too large an addition of alkali injures the veins used for the injection; too small a degree of alkali brings about blood coagulation, and leads to thrombosis: a lengthy shaking of the mixture, and standing in the dry tube brings to a toxic product, the so-called arsenic oxid, which is much more highly toxic than salvarsan.

2. It has been shown that certain illnesses of a constitutional nature can cause a supersensitiveness. Thus, for instance, tuberculosis of the suprarenal glands, the so-called Addison's disease, is an illness which, according to the observations of Wechsclmann and myself, brings about a severe supersensitiveness of the patients to arsenic compounds. The same applies to the states lymphaticus, which, as has already long been known, must be regarded as a type of the constitutional fact of resistance and supersensitiveness.

Furthermore, the seat and location of the disease may also bring about supersensitiveness, a supersensitiveness which is excited by the very reaction. We are indebted to the master mind of Robert Koch for the first knowledge of this peculiar phenomenon—the well known focal tuberculin reaction. Every year, however, occur when the parasites are rapidly dissolved in a focus filled with parasites. Then under the influence of the liberated toxin an irritation of the tissues sets in which is characterized with fever, diarrhoea and swelling, and which is known in the case of the "lactic" illnesses as "Vajarich-Recherlein's reaction." Such reactions are, of course, of great importance when in connexion with the skin; but if the reaction is to have its seat in the neighborhood of vital organs (brain), then the swelling may perhaps bring about injury of a nature serious to life, or even death itself. Indeed, it is well known that tuberculosis has in the other hand excited an exceedingly dangerous manner by the careless use of the tuberculin reaction; in spite of this, however, one will think of attributing the nervous disturbances to a neurotropism of tuberculin. And exactly the same phenomenon may occur with salvarsan if the sporochoetae of syphilis have localized themselves in the central nervous system.

As you will see, the treatment of cases is an exceedingly difficult and responsible task, and the clinical pioneers, such as Schreiber, Wechsclmann, Jevrem, and others, deserve our warmest thanks. They have thrown the first light upon the most important questions (poulsology, indications and contraindications). From a series of observations, we note so vast that it can hardly be surveyed, there have been, I might say, what are called "clinical tactics," and which I should like here briefly to explain.

1. The Thypxia sterilis is, which consists in this—that by means of one or at most two injections the body is freed from the parasites. In experiments on animals, and also in the case of a series of important maladies, this principle can be carried through in a clear and pure manner with the names of Wolif, Bobert, and Wassermann, we are in a position to recognize the specific infections early, that we must select as the first principle of medical treatment, Frapper fort et frapper vite. It is a matter of course that the necessary dose must be greater in proportion to the severity of the disease, but it is certain that a definite number of parasites is destroyed by a certain definite dose of the remedy, the quantity must be multiplied if the number of parasites—apart from the course of the disease—otherwise increases. Apart from this, by a rapid destruction of the parasites cataracts are set at liberty which, with increasing numbers of parasites, reach the circulation of the blood in ever-increasing quantities. If we consider how frequently, at the height of the disease, serious or irreparable pathological disturbances occur, such as suppurations or necroses, and these, of course, continue even when the pathogenie cause has been destroyed, and are multiply complicated, I refer here to the typhoid ulcers and to the abscesses and necroses in the case of horse sickness.

Therefore, it is in my opinion necessary to allow the therapeutic treatment to come into action as early as possible, as under these circumstances the full success is most easily and most surely attainable. And it is at the present time when, owing to the progress of diagnosis, and especially the modern assistance rendered by the microscope and serological investigations which are being connected with the names of Wolf, Bobert, and Wassermann, we are in a position to recognize the specific infections early, that we must select as the first principle of medical treatment, Frapper fort et frapper vite.

We shall now have to consider the question, What are the causes which make it possible for such a favourable result to be obtained, a result which may be taken as Thypxia magna sterilis, radical cure of the body by means of a single injection? Typical antibiotes are shown to be produced fairly rapidly by the destruction of parasites, and especially of protozoea. Hence, it is quite evident that this advantageous action of the organism ought to be eminently efficacious. For if the medicine has destroyed not the whole of the parasites, but only 35 per cent., the remaining 5 per cent. may succumb to the influence of the antibiotics which are rapidly formed. If this is the case, the Thypxia sterilis is attained. Unfortunately, it has been shown that this salutary process may be frequently minimized by the biological properties of the parasites. For it may happen that a number of the parasites which survive the first injection escape destruction by the serum either wholly or in part, and become, after a subsequent change in the serum, resistant and serum-proof, and are now known as a "relapsing crop." The possibility of forming a relapsing crop largely depends on the nature of the parasites. In the case of sporillosis of the lungs, which, as is known, is the most dangerous varieties which have become serum-proof, and are now known as a "relapsing crop," the number of relapsing relapsing relapsing crops do not seem to form, and the chemotherapeutic care is therefore an eminently easy one. In cases of recurrent or relapsing fever in human beings, the number of relapsing relapsing crops are limited to three or four.

The number of relapses which we have observed clinically corresponds exactly to the existence of the various relapsing relapsing relapsing crops. On the other hand, the patient in an extraordinarily great variety of relapsing strains, and in this connection I need only mention the trypanosome and, in particular, the parasit of human syphilis.
In collaboration with Dr. Röhl and Prof. Gulbransson, and lately with Dr. Ritz, I have been able in the case of mice to produce, and to transmit for any length of time, eight entirely different forms of gonorrhea. It is clear that when the parasites of this kind, which are able to form such a large number of relapsing crops, very great difficulties must be encountered in the treatment. The auxiliary forces of the body fail to act, so that it is next to impossible to make the utmost to destroy the whole of the parasites at once by means of drugs; owing to its great power of adaptation a single surviving germ may perhaps cause the infection to break out afresh.

Why is it that some of the germ escapes disinfection in this way? It is an exactly definable quantity of an antiseptic is added to a liquid containing bacteria, a complete disinfection takes place; not a single germ escapes the destructive influence. But such ideal conditions do not obtain in practice, in disease, as we sometimes find that in certain places, in the so-called "dead corners"--formed by gas or water pipes, and so on--the disinfecting gas does not act sufficiently. In like manner the parasites which have settled in such "dead corners" of the organism are not the reached by the disinfectants.

"Practical tests, however, have quickly taught us where such "dead corners" are to be found in the organism. The principal one is the cerebro-spinal fluid, which is the fluid which fills the spinal cord and the dura, which is filled with a liquid as clear as water and almost entirely free from cells and bacteria, unless the dura is infected. This fluid contains the cerebro-spinal fluid can only be accounted for by the fact that the cells by which it is secreted are in a high degree insusceptible to most of the constituents of the organism, although, for example, that they only permit a limited quantity of substances with small molecules to pass through. The drugs with more complex molecules are thus kept back, as albumins, and cannot get into the cerebro-spinal fluid. Therefore, parasites be lodge here, it is impossible for the drug to attack them. This localization of the parasites is of very special importance in connection with the parasyphilis diseases, tabes, and paralysis.

Another possible explanation of the defective sterilization is this: that among the large number of parasites there may be some which are unaffected by a certain drug and resist sterilization. On the whole I am of opinion that this fact does not play a very great part in the course of fresh infection, but that it becomes prominent in connection with those diseases which are characterized by innumerable relapsing outbreaks, such as sleeping sickness, leprosy, and so forth.

* * *

Here two possibilities are conceivable: First, if sleeping sickness is excited by a toxin in the usual manner, it is possible—as can be demonstrated easily by experiment—for an atoxyl-proof stock of trypanosomes to develop itself by adaptation.

* But secondly, as I have already mentioned, the more continual formation of relapsing crops, in the course of time and of several generations, can bring about a change in the chemioscopes in the parasites. This, according to circumstances, may result in either an increased or a reduced power of resistance in the parasites. For instance, I have found that a trypanosome strain which was not affected by trypan violet lost this peculiarity after having passed through a relapsing crop.

We should, of course, expect that certain relapsing crops, especially those showing a great tendency to relapse, should become much less sensitive to the original stock. And the serious influence of the usual specifics, mercury and arsenic, upon parasyphilis diseases, in connection with which Noguchi has lately proved the peculiarity of living sporia, tends to show that this is the case here.

* * *

These few facts and considerations suffice to indicate in which cases we may rely upon the result of the chemotherapeutic treatment, and in which cases they have been more successful, and in which cases such a result is to be obtained less easily and only by a circuitous road. The latter is the case with the cases with chemically curing disease having localizations not easily reached. If we consider the fight against parasitic diseases with a state of warfare, we find that, on the one hand, great battles are fought which may lead to victory in the course of one or a few days. In combating bacteria such a victory would compare with Therapia nigra sterilization. If, on the other hand, a fortress has to be taken, months and even years may be necessary.

May I be permitted at this juncture briefly to point out the aids which are employed in connection with a bacteriological sieve?

1. When parasites are lodged in a "dead corner" and are in consequence difficult to reach, it has frequently been found advisable to employ, instead of one single injection a long series of injections extending over several weeks, the so-called serial treatment, corresponding with the rule: Gutta locupletior. In this connection I would specially point to the results which Leriche de Paris and Dreyfus of Frankfurt have obtained by these means.

2. In many cases it is desirable to employ a therapeutic agent of as small a molecular volume as possible, such as muriatic, which has been successfully employed by Simon Flexner in cases of infantile paralysis.

3. Moreover, various writers (Fouquet, Litingt, etc.) have suggested rendering the epithelium of the choroidal plexuses more pervious to the therapeutic agent by means of certain chemicals, and thus making more of the therapeutic agent to get into the cerebro-spinal fluid. Unfortunately this method so far has not led to any tangible results:

4. The possibility of making direct injections into the cerebro-spinal fluid, and thus giving more of the therapeutic agent get directly to the parasites contained in this fluid has also suggested itself. Thus Ayres Kopke, of Lisbon, has injected suitable disinfectants into the cerebro-spinal canal, Swift and Morse of the Rockefeller Institute, have recently adopted a novel and interesting method in the treatment of tubercle which promises to be very valuable.

They treat the patient by first injecting salvarsan; shortly afterwards they draw blood from him, and inject considerable quantities of the serum obtained from it into the spinal canal. This method is not only novel but suitable in so far as it obviates all possible ill-effects on the sensitive central nervous system by employing serum obtained from the patient himself, while at the same time it is possible to apply the curative agent in sufficient quantities. The results obtained by this method were entirely satisfactory.

It is fairly obvious that all these measures aim at the whole at rendering the places which are not easily approached more accessible to the therapeutic agent, and that this is the case in ordinary conditions. On the other hand, however, the greater power of resistance of certain parasites has to be taken into account, and this is a purely chemical question which can be decided upon by the drug.

The road leading to its solution which promises the best results is that of combined therapy.

From what has been said it will be seen that combined therapy is best carried out with biologic drugs, which attack entirely different chemioscopes in the parasites. For instance, it is useless to combine fusidin with its nearest relatives, methyl violet, and it is useless to combine therapeutically trypan blue and fusid in red, for both attack the same spots in the parasites. But it is necessary to select from each group the most effective substance and then to combine the most suitable representatives of the various types. It is clear that in this manner a simultaneous and varied attack is directed on the parasites, in accordance with the military maxim, "March apart but fight combined.

Here the interesting fact has been brought out that, when such combinations are used, summation of the toxic properties of the various substances need not occur so far as the organism is concerned, with which we combating the parasite, the therapeutic properties are augmented.

To quote a case in point, it was found that a sulphuric-oxyphosphorous acid, which is ten times as poisonous as salvarsan, when added to salvarsan up to a certain percentage did not render the mixture more poisonous. But the healing properties of this mixture were three to four times greater than those of salvarsan in the treatment of a trypanosome infection in mice. Such phenomena are quite common in combined therapy. If one injects a mixture, for instance parasuchin and salvarsan; the original matter is gathered up at the spots of the receptors, and finds its way into one out of two, or the salvarsan into another, so that by this method an increase in the toxicity does not take place, provided the components have been
EXACTLY THE SAME FAVOURABLE RESULTS HAVE BEEN OBTAINED WITH RELAPSING FEVER, IN THE HUMAN SUBJECT, THE FEVER IMMEDIATELY SUBSIDING AFTER THE INJECTION OF SALVARAN, AND THE PATIENTS BEING CURED BY ONE INJECIION. THE VERY RARE CASES OF RECURRENCE THAT OCCASIONALLY DO OCCUR ARE EASILY CUREABLE.

TO CONTINUE DEALING WITH SALVARAN IN YAWS, WHICH IS SO CLOSELY RELATED TO FRAMBOESIA, A FAIR PERCENTAGE OF CURES HAS BEEN OBTAINED IN THE VERY LARGE BURDEN OF CASES BY A SINGLE INJECTION OF A LARGE DOSE, BUT, OF COURSE, THE ABOURATIVE CURSE BY INTENSIVE TREATMENT IS FAR MORE CERTAIN.

WHAT VINCINT’S AGINSA AND THE DISEASES OF THE MUCOUS MEMBRANE OF THE MOUTH, CAUSED BY BOCCLIPSPHACET, Therapla sterilisana magna is possible; in fact, in many cases a mere local application of salvaran suffices. I may here further mention tertian malaria. In this form, but in this form alone, salvaran has proved successful, as it has in blastomycysis (Petersen) and Alpo boil. As regards the diseases of animals which can be cured by the single injection of salvaran, I might mention the acute breast disease of horses, which is of such enormous importance to the military authorities, and lymphangetic spirophon, the African glands in horses.

WHAT IMPORTANTE AND MOST NICE OBSERVATIONS OF ROGERS, WHO FOUND EMBRIOS TO BE A SPECIFIC AGAINST THE VERY SERIOUS AMOEBAE DISEASE. AND IF HERE IT IS INDICATED AND OR NECESSARY TO REPEAT THE INJECTIONS, YET THE INJECTIONS REMAIN UNAFFECTED: IT IS ALL ONE TO THE PATIENT AS TO WHETHER THERAPLA STERILISANA MAGNA OR THERAPLIN STERILISANAE FRANCF prolong, it only being, provided only he is relieved of his suffering in a harmless manner.

Tropleasias also, which causes serious disease in cattle and dogs, may, according to the observations of Nuttall, be favourably influenced. Tropleasias does of quinine are no longer able to destroy the parasites. If, however, such a patient receives an injection of salvaran, the malaria parasites are destroyed at once, for although these may be quinine-proof, they are not salvaran-proof. Should the doses of salvaran have been too small to prevent a relapse, and provided further doses of quinine are given to the patient when parasites are present, the quinine effect may be obtained by means of quinine. Consequently the combination of quinine and salvaran has the effect of neutralizing or minimizing the quinine-proof qualities of the parasites.

For all these reasons I think that combined therapy will in the future conquer an ever-increasing field of action. Thus, for instance, Broun, in the treatment of patients with malaria in whom the parasites are no longer destroyed by the quinine, the injection of salvaran will be particularly beneficial, as the parasites will then be destroyed by the quinine or its derivatives before they can become immune. And in this case the patient will be cured in a shorter time, or the dose of quinine may be reduced.

And on this account combined therapeutics are characteristic beyond contrast and neutralize those which may be said to act rather in one single direction.

And now gentlemen, may I be permitted to refer to a few practical results? You are all aware that with a number of spilial diseases the principle of Therapla sterilisana magna is to be of most assistance. You are aware that it is possible by one single injection of salvaran to cure frambioza (yaws), which is caused by spirchaeates and is a scourge of the tropics, to which we are compelled to return on many important relapsing occur; this has been shown by the work of Strong, Koch, and Castellani. Thus in Surnam a hospital in which over 350 patients with frambioza were treated with the name of Proust was opened and turned to other uses after the introduction of the salvaran treatment, as one single injection sufficed to cure the disease, and all the patients but two could be discharged. This is to be hoped that in this way it will be possible to exterminate frambioza altogether.

properly selected. In this case the salivary glands and submaxillary are concentrated in the parasites, and their effects can consequently be added, or, in favourable cases, can be multiplied. We thus obtain the therapeutic inequality $\frac{1}{4} + \frac{1}{4} = \frac{1}{2}$.

We maintained this point for quite a long time, and some very remarkable stories upon the subject—in which stress is laid on the suitability of multiple, tertiary, and quaternary concomitants—have recently appeared from Morgenroth's laboratory.

Moreover, according to more recent experiments, it seems advisable, in all cases where antiseptics are powerless, to incorporate them into a combination, because the antiseptics require a receptor apparatus entirely different from that of the chemio-receptors. Thus the combination of pneumococcal serum with methyldopa as a new body, discovered simultaneously at my institute that extends its action in combination with a dressing of antiseptic serum and salvaran.

Thus the value of the combinations is clearly shown. They make it possible, always assuming that suitable substances are used, to effect a cure with the smallest possible doses and in the least harmful manner, and to eliminate any danger resulting from a maximum dose of one of the ingredients, as a change of combination therapy is this, that under the influence of two different medicaments the danger of rendering the parasites immune to arsenic, naturally a very great obstacle in connexion with further treatment, is apparently minimized. Thus it has been shown that, in the course of a prolonged quinine treatment, it may happen—the cases are, fortunately not very frequent—that the malaria parasites become quinine-proof, whereas large doses of quinine are no longer able to destroy the parasites. If, however, such a patient receives an injection of salvaran, the malaria parasites are destroyed at once, for although they may be quinine-proof, they are not salvaran-proof. Should the doses of salvaran have been too small to prevent a relapse, and provided further doses of quinine are given to the patient when parasites are present, the quinine effect may be obtained by means of quinine. Consequently the combination of quinine and salvaran has the effect of neutralizing or minimizing the quinine-proof qualities of the parasites.

For all these reasons I think that combined therapy will in the future conquer an ever-increasing field of action. Thus, for instance, Broun, in the treatment of patients with malaria in whom the parasites are no longer destroyed by the quinine, the injection of salvaran will be particularly beneficial, as the parasites will then be destroyed by the quinine or its derivatives before they can become immune. And in this case the patient will be cured in a shorter time, or the dose of quinine may be reduced.

And on this account combined therapeutics are characteristic beyond contrast and neutralize those which may be said to act rather in one single direction.

And now gentlemen, may I be permitted to refer to a few practical results? You are all aware that with a number of spilial diseases the principle of Therapla sterilisana magna is to be of most assistance. You are aware that it is possible by one single injection of salvaran to cure frambioza (yaws), which is caused by spirchaeates and is a scourge of the tropics, to which we are compelled to return on many important relapsing occur; this has been shown by the work of Strong, Koch, and Castellani. Thus in Surnam a hospital in which over 350 patients with frambioza were treated with the name of Proust was opened and turned to other uses after the introduction of the salvaran treatment, as one single injection sufficed to cure the disease, and all the patients but two could be discharged. This is to be hoped that in this way it will be possible to exterminate frambioza altogether.
ADDRESS ON HEREDITY.

Delivered at the Seventeenth International Congress of Medicine.

By W. Batson, M.A., F.R.S.

Let me on behalf of my colleagues, the students of genetics, express our deep sense of the honour which has been conferred upon us by the organization of your Congress in choosing as the subject of one of the general addresses. It is scarcely necessary that I should say, on my own behalf, that I feel it an extraordinary privilege to be permitted to represent that science on such an occasion.

This is a great privilege, but it entails also a very grave responsibility. Conscious as we are of the practical and theoretical significance that the study of heredity must begin to assume, it would be mere affectation were I to suggest any mitigating as to the propriety of allotting to this subject a prominent position in your deliberations.

To the penetrative foresight of Francis Galton it was evident long ago that these aspects of physiology must one day become one of the chief preoccupations of reflecting minds. That inference has drawn from a broad contemplation of the facts of descent. Traces of order among these phenomena lie directly within our own immediate experience, and yet the poor and ingenuously patient half-century-long work of our forefathers has brought us to the present position.

But great as is the service rendered by the scientific interpretation of the phenomena of descent, it is clear that the results of these investigations are even more valuable, and that a satisfying knowledge which has been given to genetic science a position paramount among the branches of biology, owing to the growing investigation in the departments of the human heredity, is already available to the medical and physiological sciences. There is no more important subject in the whole range of biological science than the study of heredity, and yet we find in all the fields of science that the knowledge of the laws which govern the inheritance of characters is almost entirely confined to this one branch of physiology.

It is true that the methods of study are much more difficult, and the results much less certain, than in other sciences, but it is certain that the methods of investigation are rapidly improving. The results of the work of the past few years have shown that the inheritance of characters is not only governed by the laws of probability, but that the laws of probability are themselves subject to the laws of inheritance. The study of heredity is therefore a science of enormous importance, and it is a science which is rapidly becoming more and more important.

The study of heredity is a science of enormous importance, and it is a science which is rapidly becoming more and more important. The results of the work of the past few years have shown that the inheritance of characters is not only governed by the laws of probability, but that the laws of probability are themselves subject to the laws of inheritance. The study of heredity is therefore a science of enormous importance, and it is a science which is rapidly becoming more and more important.

[The Benett Memorial Lecture]