

Address in Pathology, ON CHEMIO THERAPY.

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BY

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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 wondering admiration round Lord Lister, who through his introduction of antiseptics 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 modern institute for tropical diseases, 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 hygienic struggle against tropical and subtropical diseases. Castellani's proof that a trypanosome causes sleeping sickness, the classical 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 Plimmer 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 opsonins and on the prophylactic treatment of typhoid fever, carried out in so practical and excellent a manner. Even these few 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 infectious diseases. To prevent the spread of and to heal infectious disorders has 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 therapeutics chemotherapy has, indeed, been in existence, as all the remedies which we employ are chemicals; on the other hand, experimental chemotherapy could only develop 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 chemiotherapeutic research. The whole area is governed by a simple—I might even say natural—principle. If the law is true in chemistry that *Corpora non agunt nisi liquida*, then for chemiotherapy the principle is true that *Corpora non agunt nisi fixata*. When applied to the special case 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 "parasitotropic." But I should like immediately 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 subcutaneous tissues which is 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 chemiotherapy not to build on the basis 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 parasitocides, 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 antistances. 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, spirochaetes—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 Hata, the conclusion has been drawn that salvarsan or neo-salvarsan, as such, did not in any way influence the spirochaetes directly. Now it can very easily be shown that this conclusion is quite incorrect. If, for instance, following Castelli, one suspends the spirochaetes of relapsing fever in indifferent mixtures of serum which do not injure their vitality, and if one fills two small tubes therewith and adds to one of the tubes a very small quantity of salvarsan or neo-salvarsan, and if one then centrifugalizes and next draws off the liquid; if one washes the remaining spirochaetes again in a mixture of serum and again centrifugalizes it; then one obtains in each tube a deposit of spirochaetes which on microscopic examination show an equal degree of mobility. If, however, the spirochaetes obtained in this manner are injected into test mice, then one can very soon convince oneself that the spirilla 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 spirochaetes, 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 in the animal body. By this very simple and easily intelligible experiment, therefore, the direct effect of salvarsan and neo-salvarsan on the spirochaetes, and thereby the principle of fixation, is absolutely proved; so the objection that the effect is indirect and due to antistances falls to the ground.

It was necessary, however, to penetrate more deeply into the mechanism of this fixation of remedies. It is only after long-continued efforts that a clear conception has been successfully obtained. In order to make practical progress it appeared necessary not to be satisfied with the primitive idea, but to see in what manner the drugs actually are fixed by the parasites or by the cells, as the case may be. Only by taking a very roundabout way has it been possible to obtain clearness with respect to these complicated relations, and in this connexion it was especially the studies on trypanosomes, particularly the investigation of "drug-fast" strains of germs, which led to quite definite knowledge with regard to the process of fixation. By continued treatment of the experimental mice with certain definite remedies—for example, fuchsin—it was easy to obtain at last a race of trypanosomes which had become immune to these remedies, that is, "drug-fast," immune to fuchsin, in the case mentioned above. There were three particular classes of different remedies which were well suited to this purpose:

1. The class of the arsenic compounds (in the following historical order): Arsenious acid, arsenilic acid (atoxyl), arsenophenylglycin (salvarsan and neo-salvarsan).
2. The class of the so-called azo-dyes (the trypan red, manufactured by Weinberg, with which Shiga and I made experiments, and the trypan blue of Mesnil).
3. Certain basic triphenylmethane dyes (fuchsin, methyl violet, etc.).

When a race of trypanosomes has been rendered immune to fuchsin, then this race is immune to all the allies of fuchsin and methyl violet, but is not immune to the two other classes. 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 a definite 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 toxins and antitoxins—pointed 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 component parts of the cell—side-chains—which I have characterized as “receptors,” and that the antistances represent nothing else than the cell receptors, produced in excess under the influence of the toxin 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 it was especially the brilliant investigations by Langley relating to the effects of alkaloids which caused my doubts to disappear and made the existence of chemio-receptors seem probable to me.

From this point of view the phenomena observed in connexion with the “drug-fast” strain of germs can be readily explained experimentally, owing to the fact that the chemioreceptors under the influence of drug-fastness suffer a reduction of their affinity for certain groupings 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 arsenic compound become necessary for the destruction of a race of arsenic-fast trypanosomes, for example, for the smaller avidity can only be overcome by a corresponding surplus 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 there are present *different specific chemio-receptors*, for instance, the *arseno-receptor*, which fixes the trivalent group of arsenic as such; and the *aceto-receptor*, which fastens to itself the acetic acid group, an *iodine-receptor*, an *orthoamidophenol-receptor*, which conditions the fixation of the salvarsan, and many others in addition. A complete exhaustive knowledge of all the different chemioreceptors of a certain definite parasite is what I should like to characterize as the *therapeutic physiology of the parasite cell*, and this is a *sine qua non* of any successful chemiotherapeutic treatment. I should like to emphasize the fact that many observations indicate that certain chemioreceptors are due to several different kinds of parasites, not to a single one. The knowledge of these is of special practical importance, because remedies which are adjusted to these have a healing influence on a very large series of the most various pathogenic agents. *The larger the number of different chemioreceptors, therefore, which can be demonstrated, the greater is the possibility of a successful chemiotherapy.*

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 chemioreceptors of the parasite. This is only a necessary prior condition of the toxic effect, 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, and is described as *haptophoric*, there must be 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 views which we have long maintained with respect to toxins, in which we distinguish the presence of a *haptophoric* group which conditions the cell fixation and also the formation of the antitoxins, and a *toxophoric* group which brings about the injurious action on the cell. In the case of the highly complicated synthetic drugs the assumption will have to be made that the *haptophoric* group and the *toxophoric* group are not *directly* connected

with one another, but are linked with a chemical molecule in the character of side-chains as separate groups. In this way we come naturally to this, that chemiotherapeutic agents, built up in a complicated manner, may be compared to a poisoned arrow; the fixing group of the drug which anchors itself to the chemioreceptor of the parasite corresponds to the point of the arrow, the binding member is the shaft, and the poisonous group is the poison smeared on the arrow's head. Corresponding to this scheme in the case of salvarsan (dioxydiamidoarsenobenzol) the benzol group would correspond to the shaft, the orthoamidophenol group 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 so 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. The circumstance that all the derivatives of arsenic which contain arsenic in the pentavalent form, that is, in the fully saturated form, do not bring about any therapeutic action, but that this only commences when the arsenic atom exists in the unsaturated trivalent condition, certainly points in the same direction. This difference between the saturated and unsaturated arsenic compounds was discovered by the master mind of Bunsen, for in the year 1843, in his comparative studies relating to the non-poisonous cacodylic acid with the pentavalent arsenic, and its poisonous reduction product the cacodyl with the trivalent arsenic, he came to the conclusion that “the cacodylic acid had lost the power to form an attacking point, and at the same time it had lost its effect on the organism.” In later times many analogous cases pointing to the increased effectiveness of the unsaturated compounds have become known. The best known example is doubtless the high toxicity 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 unsatisfied avidities which render them capable of making addition compounds with other bodies.*

If, therefore, we poison a spirochaete with salvarsan, then there occur at least two different chemical fixations. First of all, the fixation of the orthoamidophenol group, which primarily fixes the salvarsan to the parasite. It is only in consequence of this fixation that, secondarily, the trivalent arsenic group is given the opportunity of entering 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 react if favouring factors, which from the chemical point of view must be regarded as stereochemical facilitation, come into action.

Examples of such stereochemical facilitations are frequently found in the chemistry of the ortho-condensations, for example. And so the haptophoric group of the arsenic molecule primarily brings the arsenic to the cell, and secondarily brings about its possibility of action.

Now, it is a frequent practice of many uncivilized 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. In association with Dr. Karrer I succeeded in attaching 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 previous remarks I have described the conditions which are necessary if a certain substance is to exert a parasitocidal effect, and indeed must effect such, if it operates directly on certain definite parasites in an aqueous solution, as, for instance, is the case with the ordinary disinfectants. In the manner described above it is easily possible to produce a very large

number of substances which will destroy bacteria and allied substances in aqueous solutions. But, of course, the problem is much more difficult when it is a question of internal disinfection or of the destruction of living parasites within the infected organism. If the problem of sterilizing a room is set before us, then indeed it is easy to do so, owing to the present advancement of science. But the task becomes more difficult when the room is filled up with materials; and when these materials are of such a delicate sensitiveness as living cells, then the difficulty of the problem will be manifest without any further explanation. As a matter of fact, it has proved that substances which, even when highly diluted, bring about a colossal bactericidal effect in aqueous solutions are totally ineffective in therapeutics properly so called. For it has turned out that, generally speaking, these disinfectants are more or less powerful cell poisons, and seriously injure the organism; they are therefore not only parasitotropic but also organotropic.

Now, it depends exclusively on the relationship between the parasitotropism and organotropism whether a certain disinfectant can be used as a remedy. In Robert Koch's celebrated experiment, in which even the largest doses of sublimate did not produce a trace of therapeutic effect on anthrax infection, it is evident that the parasitotropic effect was reduced to *nil* by the organotropic effect. If the relationship of organotropism to parasitotropism is somewhat more favourable, then one may observe a peculiar phenomenon, consisting in the course of the infection being rendered worse to an extraordinary degree by the remedy, owing to the effect that the parasites increase to a much greater extent than is the case when no disinfecting agent is employed.

This phenomenon, discovered by Hata, is explained by the fact that the ratio of organotropic effect to parasitotropic effect is of such a nature that almost the whole of the poison is absorbed by the organism, but only an infinitesimal quantity by the parasites. According to a fundamental biogenetic principle it is quite a common thing for substances which act destructively in large quantities to bring about an increase in the vital functions when given in smaller doses. The only substances, therefore, that can be used as therapeutic agents are those in which the ratio between organotropic effect and parasitotropic effect is a favourable one, and that can be easily ascertained by experimental comparison of the *dosis toxica* with the *dosis tolerata*. The only substances that can be considered therapeutic agents are those of which a fraction of the *dosis tolerata* is sufficient to bring about therapeutic effects.

The organotropic effect of drugs is of course to be attributed, according to the views of Langley and myself, to this; that there are in the most various cells of the body and its organs quite different chemioreceptors, exactly in the same manner as we have 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 mention here—in order only to indicate a few examples—the intra-vitam staining of the nerve trunks by methyl blue, the staining of the cell granules by neutral red, and the distribution of isamin blue in the so-called pyrrol cells so carefully and excellently investigated by Edwin Goldmann. The pathologico-anatomical findings point also to a chemical divergence on principle. When we see that after the introduction of paraphenylenediamine only the summit of the diaphragm assumes a black colouring; when we see that vinylamine in the case of all kinds of animals isolates and injures the renal papillae and causes them to die; when after the introduction of cyanosin, as Hata and Goldmann have found, certain definite regions in the hair of mice become coloured, and the colouring matter becomes stored to the greatest degree in the milk glands; when a colouring material of the pyronin series in the case of mice brings about a general dropsy, amounting to 50–60 per cent. of the body weight without injuring the kidney, a phenomenon that doubtless is only to be referred to an alteration of the vessels of the subcutaneous connective tissue; then all these phenomena can only be explained by the fact that at these particular spots definite chemical unions of a specific nature must take place, and must be referred to the presence of certain definite chemioreceptors.

Now, according to the above views, all these fixations are dependent on the haptophoric grouping of the drugs. It was therefore a matter of great interest to observe how phenylarsenic acid, the mother-substance of the modern arsenic compounds, behaves when various different atomic groups are attached to it. In this connexion it has been found that when we introduce different fixation groups—for example, chlorine, the oxygen group, the hydrocyanic 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 combinations which are to the greatest extent free from poison—these are derivatives of sulphuric acid, especially the sulpho-phenylarsenious acid and its salts—are less toxic than sodium chloride. On the other hand there are substances the very smallest quantity of which brings about death. And in this connexion we can see that, according to the nature of the substances, very different organs of the animal's body are injured. Sometimes it is the intestinal tract, and the animals die of profuse diarrhoea; sometimes it is the liver, and the mice—a rare occurrence—become jaundiced, and die of serious alterations in the liver; sometimes the red blood corpuscles become dissolved, and the animals die of severe anaemia. Frequently also the central nervous system becomes injured, and in the case of mice the vestibular nerve of the internal ear. The interference with the equilibrium 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 optic nerve is the point of attack for numerous derivatives of phenylarsenious acid. The cases of blindness which have been observed after the use of very large doses of atoxyl, arsacetin, and other drugs, are due to analogous injuries.

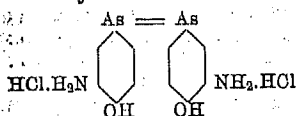
From this it is evident that according to the selection of the group combined with the phenylarsenious acid, quite different organs will be affected. According to the above views this is only explained by the fact that there are, as already previously stated, in the various organs specific chemioreceptors which energetically attract certain fixation groups somewhat as a magnet attracts iron. And this view also provides us with the principle according to which we have to construct our poisoned arrows. We must attach to the phenylarsenious acid group, or, as the case may be, to the phenylarsenobenzol group, such an atomic group as is but distantly related to the organs of the sick body, but on the other hand is chemically very closely allied to the receptors of the parasites.

I have explained above that the parasites possess a whole series of chemioreceptors which are specifically different from one another. Now if we can succeed in discovering among them a grouping which has no analogue in the organs of the body, then we should have the possibility of constructing an ideal remedy by selecting a haptophoric group specially adjusted to the functions of the parasites.

A remedy provided with such a haptophoric group would be entirely innocuous in itself, not being fixed by the organs. It would, however, strike the parasite with full intensity, and in this sense it would correspond to the immune productions, the antistances discovered by Behring, that fly in search of the enemy after the manner of the bewitched bullets. Let us hope that it will be possible chemiotherapeutically to hit the bull's eye in this manner also. I do not consider this at all out of the question, as it may be proved in certain diseases—spirillosis in hens, for example—that from the fiftieth to the hundredth part of the *dosis tolerata* of salvarsan entirely frees the animals from the parasites and leads to a cure. Such a dose truly represents a negligible quantity, as the hen cannot be damaged thereby in the slightest degree. But such favourable conditions have only very rarely been discovered up to the present; we shall have to be satisfied if we can succeed in obtaining good therapeutic results with the tenth or even the fifth or sixth portion of the *dosis tolerata*.

In the main the above are the principles which guided us in the construction of the new remedies. Many combinations have been tested in experiments on animals in the case of trypanosomes and spirillar infection. In their preparation I have been supported by the untiring co-operation of Dr. Benda, Dr. Berthelm, Dr. Kahn, and Dr. Karrer, and they have been biologically tested, especially

by my respected friend Professor Dr. Hata, and later by Dr. Gastelli and Dr. Gonder and Erl. Leupold. Salvarsan has proved to be the most efficient, the dioxydiamidoarsenobenzol dichlorhydrate of the formula



Here the orthoamidophenol group acts as the conducting and the arsenio group as the toxophoric group.

But now, gentlemen, the step from the laboratory to practice—to the bedside—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 men 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, crabs, etc., brings about unpleasant skin eruptions, and almost half the known remedies can incite such phenomena of supersensibility. It will not be a cause of surprise, therefore, that such phenomena may occur in a particularly serious form with the employment of therapeutic agencies which contain such powerfully acting radicals as arsenic and mercury. I 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 supersensibility in the case of salvarsan is one of the very rarest phenomena, and that it was perhaps due to a number of other circumstances, sources of error of a hidden nature, which in many cases have led to the mistaken idea that supersensibility existed. In this place we must first of all mention Wechselmann, McIntosh and Fildes, Hort and Penfold, who have brought forward the very important proof that the destroyed bodies of bacteria which may occur in sterilized water 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 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 solutions and standing in the air oxidize the drug to a toxic product, the so-called arsenic oxide, which is much more highly toxic than salvarsan.

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

Furthermore, the seat and location of the disease may also bring about supersensibility, a supersensibility which is excited by the so-called "local 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. Exactly similar reactions may, 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 connected with hyperaemia and swelling, and which is known in the case of the "luetical" illnesses as "Järisch-Herxheimer's reaction." Such reactions are, of course, of no great importance when in connexion with the skin; but if the reacting centres have their seat in the neighbourhood 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 tuberculous meningitis may be influenced in an exceedingly dangerous manner by the careless use of the tuberculin reaction; in spite of this, however, no one will think of

attributing the nervous disturbances to a neurotropism of tuberculin. And exactly the same phenomenon may occur with salvarsan if the spirochaetes of syphilis have localized themselves in the central nervous system.

As you will see, the treatment of patients is an exceedingly difficult and responsible task, and the clinical pioneers, such as Schreiber, Wechselmann, Iversen, and others, deserve our warmest thanks. They have thrown the first light upon the most important questions (posology, indications and contraindications). From a series of observations, now so vast that it can hardly be surveyed, there have, however, resulted what I might call the "therapeutic tactics," and which I should here like briefly to explain.

1. The *Therapia sterilisans magna*, 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. Here, therefore, the old therapeutic motto is applicable: *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, for it is absolutely clear that if 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—as happens during the course of the infection—has likewise multiplied. Apart from this, by a rapid destruction of the parasites endotoxins are set at liberty which, with increasing numbers of parasites, reach the circulation of the blood in ever-increasing concentration. And then, frequently, at the height of the disease, serious or irreparable pathological disturbances occur, such as suppuration or necrosis, and these, of course, continue even when the pathogenic cause has been destroyed, and may lead to unpleasant complications. 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 just 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 connected with the names of Widal, Rubner, 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 vite*.

We shall now have to ask ourselves 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 *Therapia magna sterilisans*, radical cure of the body by means of a single injection? Typical antibodies can be shown to be produced fairly rapidly by the destruction of parasites, and especially of protozoa. Hence, it is quite evident that this adjuvant action of the organism ought to be eminently efficacious. For if the medicine has destroyed not the whole of the parasites, but only 95 per cent., the remaining 5 per cent. may succumb to the influence of the antibodies which are rapidly formed. If this is the case, the *Therapia sterilisans magna* is attained. Unfortunately, it has been shown that this salutary process may frequently be 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 subsequently change into new varieties which have become 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 spirillosis of fowls, which, as is known, is a disease taking a typical course, relapsing crops do not seem to form, and the chemiotherapeutic cure is therefore an eminently easy one. In cases of recurrent or relapsing fever in human beings, the number of the relapsing crops is restricted to three or four. The number of relapses which we have observed clinically corresponds exactly to the existence of the various relapsing strains. On the other hand, other parasites can exist in an extraordinarily great variety of relapsing strains, and in this connexion I need only mention the trypanosomes and, in particular, the parasite of human syphilis.

In collaboration with Dr. Röhl and FM. Gulbransen, 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 growths. It is clear that with parasites of this kind, which are able to form such a large number of relapsing crops, very great difficulties must occur in the treatment. The auxiliary forces of the body fail to act, so that it is necessary to do one's utmost to destroy the whole of the parasites all 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 germs escape disinfection in this way?

If 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 living organisms. Even in disinfecting a room 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 reached by the drug.

Practical tests, however, have quickly taught us where such "dead corners" are to be found in the organism. The principal one is the hollow situated between the spinal cord and the dura, which is filled with a liquid as clear as water and almost entirely free from cells and albumin, the cerebro-spinal fluid. This condition of 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 impervious to most of the constituents of the organism, albumin, for example, and 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 albumin is, and cannot get into the cerebro-spinal fluid. Should, therefore, parasites be lodged here, it is impossible for the drug to attack them. This localization of the parasites is of very special importance in connexion with the parasymphilitic 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 certain drugs 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 connexion with those frequently recurring diseases which are characterized by innumerable relapsing outbreaks, such as sleeping sickness, lues; and so forth.

Here two possibilities are conceivable: First, if sleeping sickness, for example, is treated with atoxyl 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 mere continual formation of relapsing crops, in the course of time and of several generations, can bring about a change in the chemioreceptors 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 red 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 than the original stock. And the serious influence of the usual specifics, mercury and arsenic, upon parasymphilitic diseases, in connexion with which Noguchi has lately proved the presence of living spirilla, tend 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 chemiotherapeutic treatment being entirely and rapidly successful; and in which cases such a result is to be obtained less easily and only by a circuitous road. The latter is especially the case with chronically recurring disease having localizations not easily reached. If we compare 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 magna sterilisans*. If, on the other hand, a fortress has to be taken, months and even years may be required.

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

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, in accordance with the rule: *Gutta cavat lapidem*. In this connexion I would specially point to the results which Leredde of Paris and Dreyfus of Frankfurt have obtained by these means.

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

3. Moreover, various writers (Touton, Duhot, etc.) have suggested rendering the epithelium of the choroidal plexuses more pervious to the therapeutic agent by means of certain chemicals, thus causing 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 canal, in order to let more of the therapeutic agent get directly to the parasites contained in the fluid has also suggested itself. Thus Ayres Kopke, of Lisbon, has injected suitable disinfectants into the cerebro-spinal canal; Swift and Moore, of the Rockefeller Institute, have quite recently adopted a novel and interesting method in the treatment of tabes 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 on the whole at rendering the places which are not easily approached more accessible for the therapeutic agent than 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 only be solved by chemical means. 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 therapeutic agents which attack entirely different chemioreceptors in the parasites. For instance, it is useless to combine fuchsin with its nearest relative, methyl violet; and it is useless to combine therapeutically trypan blue and trypan 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, whilst, so far as concerns the parasite, the therapeutic properties are summated. To quote a case in point, it was found that a sulphite of p-oxyphenylarsenic 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 para-fuchsin and salvarsan, the colouring matter is stored up by one set of receptors, and finds its way into one set of organs, the salvarsan into another, so that by this method an increase in the toxicity does not take place, provided the components have been

properly selected. In this case $\frac{1}{2} + \frac{1}{2}$ is not equal to 1, so far as concerns affection of the organs, but smaller than 1. On the other hand, both substances are concentrated in the parasites, and their effects can consequently be added, or, in favourable cases, can be multiplied. We thus obtain the therapeutical inequality $\frac{1}{2} + \frac{1}{2} + \frac{1}{2} = 1$.

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

Moreover, according to more recent experiments, it seems advisable, in all cases where antisubstances are produced, systematically to incorporate these same in the combination, because the antisubstances require a receptor apparatus entirely different from that of the chemio-receptors. Thus the combination of pneumococcal serum with methylhydrocuprein, as tried by Morgenroth, has proved very efficient in connexion with tests on animals executed by Neufeld, while Dr. Bierbaum discovered simultaneously at my institute that exactly the same holds good in connexion with a combination of dysentery serum and salvarsan.

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. A further advantage of combined 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, so that therapeutical doses of quinine are no longer able to destroy the parasites. If, however, such a patient receives an injection of salvarsan, the malaria parasites are destroyed at once, for although they may be quinine-proof, they are not arsenic proof. Should the doses of salvarsan have been too small to prevent a relapse, and provided further doses of quinine are given to the patient when parasites again appear in the blood, a curative effect may be obtained by means of quinine. Consequently the combination of quinine and salvarsan 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, Broden, in the Congo, while treating sleeping sickness in the human subject—it is true only in the early stage of this intractable infection—succeeded in obtaining good results by the combination of salvarsan and two basic colouring matters (trypanavin and trypanosan), the treatment lasting about a week.

It is precisely in the manifold possibilities of combination that I see a special advantage, and peculiar potentialities of development. When once we are acquainted with the majority of the chemioreceptors of a particular kind of parasite—a long piece of work occupying many hands and many heads—we shall have far-reaching possibilities of simultaneous attack by various agencies. And on this account combined therapeutics are characteristically pluralistic in contrast to the anti-toxins, 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 spirillar diseases the principle of *Therapia sterilisans magna* has proved most successful. You are aware that it is possible by one single injection of salvarsan to cure framboesia (yaws), which is caused by spirochaetes and is a scourge of the tropics, to cure it completely except in rare cases where unimportant relapses occur; this has been shown by the work of Strong, Koch, and Castellani. Thus in Surinam a hospital in which over 300 patients with framboesia were constantly under treatment was closed and turned to other uses after the introduction of the salvarsan treatment, as one single injection sufficed to cure the disease, and all the patients but two could be discharged. It is to be hoped that in this way it will be possible to extirpate framboesia altogether.

Exactly the same favourable results have been attained with relapsing fever in the human subject, the fever immediately subsiding after the injection of salvarsan, and the patients being cured by one injection. The very rare cases of recurrence that occasionally occur are also readily curable.

To continue dealing with salvarsan in syphilis, which is so closely related to framboesia, a fair percentage of cures has been obtained in the very first stage of the disease by a single injection of a large dose, but, of course, the abortive cure by intensive treatment is far more certain.

With Vincent's angina and the diseases of the mucous membrane of the mouth, caused by buccal spirochaetes, *Therapia sterilisans magna* is possible; in fact, in many cases a mere local application of salvarsan suffices. I may here further mention tertian malaria. In this form, but in this form alone, salvarsan has proved successful, as it has in blastomycosis (Petersen) and Aleppo boil. As regards the diseases of animals which can be cured by a single injection of salvarsan, I might specially mention breast disease of horses, which is of such enormous importance to the military authorities, and lymphangitis epizootica, the African glanders in horses.

Most important are the recent observations of Rogers, who found emetine to be a specific against the very serious amoebic dysentery. And if here it is indeed advisable and necessary to repeat the injections, yet the triumph of therapeutics remains unassailed; it is all one to the patient as to whether *Therapia sterilisans magna* or *Therapia sterilisans fractionata* is employed, provided only he is relieved of his sufferings in a harmless manner.

Piroplasmosis also, which causes serious disease in cattle and dogs, may, according to the observations of Nuttall, be favourably influenced by a pigment belonging to the class of trypan-colouring matters—namely, by trypan blue, first made by Mesnil. As I am informed, the fight against this disease has been taken up in a general manner at Pretoria under the auspices of Theiler. The injections are there performed not by veterinary surgeons, but by the farmers themselves, and they are glad to keep their valuable animals free from this serious disease.

It is indeed easy to understand that the schizomycetes, which in themselves are so much harder than the tender protozoa and spirochaetes, will offer an increased resistance to the attack of drugs. Naturally here, too, there are fine differences, and it is perhaps no accident that the pneumococcus, the protoplasm of which is, of course, most sensitive, should in the course of treatment also have shown itself to be particularly sensitive. (I refer here to the fine researches of Morgenroth in the treatment of laboratory animals, infected with the pneumococcus, by means of derivatives of quinine, especially ethylhydrocuprein.) But in the case of hardier bacteria, too, such as the *Bacillus typhosus*, the possibility of sterilization is not beyond hope. The first successful experiments in this sphere were carried out by Conrad on rabbits and later confirmed and extended by Uhlenhuth and his fellow workers.

If I briefly allude to the very hopeful experiments of Griffin Linden, who has endeavoured to influence tuberculous infections favourably by means of combinations of copper and lecithin, and if I add that salvarsan also has been shown to have a beneficial action upon the malignant anthrax bacillus, and upon that of glanders and, possibly, upon that of erysipelas, both in animal experiments, and occasionally, too, in human cases, then all that we know about the chemiotherapeutics of the specific bacterial diseases has been told, so that it is just in this direction that there lies a wide field still to be worked. This field, important as it is, is still in the very first stages of experimentation.

And if after what has been said we cast a glance over the development of medicine, and especially of the fight against infectious diseases, we must recognize that in the last fifty years the most important advances have been made in every direction, advances connected above all with the names of Pasteur, Robert Koch, and von Behring.

On the one hand, we have the isolation of the pathogenic bacteria, which was made possible really by the Koch method of the solid culture medium, and in which Robert Koch's pupils and fellow workers—Löffler, Gaffky, Pfeiffer—first participated; the study of protozoa, which

started from Laveran's discovery of the germ of malaria; the discovery by Löffler and Frosch, Roux and Nocard, of the viruses which pass through filters; and the recognition of insects as intermediate hosts and transmitters of infectious diseases, connected with the name of Theobald Smith, which has led to the most important consequences.

On the other hand, we have the study of the immunity theory which was first inaugurated so brilliantly by Metchnikoff and received a new impetus from the wonderful discovery of antitoxins by von Behring. A wide new field—that of the science of immunity and the investigation of serums—was opened up, and here Pfeiffer, Bordet, Widal, Wassermann, and many others including myself, have worked with successful result. Some of the most valuable fruits of these labours, from a practical point of view, have been the diagnosis of diseases, first in the form of the Widal-Grüber reaction, and later the Wassermann syphilis reaction; the importance of which for diagnostic and therapeutic value cannot be over-estimated.

All these discoveries, especially in regard to the ways of spreading disease by infecting agents, have, in accordance with the principle that "prevention is better than cure," been made good use of in the fight against epidemics and for prophylactic measures, and have brought about an improvement surpassing expectation. In the second place the struggle with diseases which have already broken out has benefited by these discoveries, the most wonderful example being antidiphtheritic serum.

Epidemics and other diseases are much less dangerous nowadays than they used to be. The efforts of chemiotherapeutics must be directed as far as possible to fill up the gaps left in our defences, more especially to bring healing to diseases in which the natural powers of the organism are insufficient. And I believe that now definite and sure foundations have been laid for the scientific principles and the method of chemiotherapeutics, the way is visible before us—a way not always easy but yet practicable. In the diseases due to protozoa and spirilla extraordinarily favourable results have already been gained, as I have shown. There are many valuable indications that in a series of other diseases—small-pox, scarlatina, typhus exanthematicus, perhaps also yellow fever, and, above all, the infectious diseases caused by invisible germs—the prospects of success are brightening. But in contradistinction to the protozoan disorders the ordinary or common bacterial diseases (diseases due to the streptococcus and staphylococcus, *B. coli*, typhoid and dysentery, and above all tuberculosis) will not be vanquished without a hard struggle. Nevertheless, I look forward with full confidence to this development also, and, without being set down as an optimist, will put forward the view that in the next five years we shall have advances of the highest importance to record in this field of research. There are indeed problems which often prove too great for the powers of individuals, and can only be solved by a many-sided effort. Considering the enormous number of chemical combinations which must be taken into consideration in the struggle with disease, it will always be a caprice of chance or fortune or of intuition that decides which investigator gets into his hands the substances which turn out to be the best for fighting the disease, or who it is that happens on the basal substances for the discovery of such. But the chances in favour of finding a real cure, and so of winning the big prize, will naturally increase with the number of those who occupy themselves with the problem. It is just here that we should unite our forces; and special importance attaches to that motto, *Viribus unitis*, which gives guidance in so many other fields. For this is the noble legend on the flag of this great International Congress, to which thousands have been drawn from all lands to bear testimony to the fact that in the world of science all national barriers have fallen.

THE Government of Ontario having instituted the post of inspector of the feeble-minded has appointed thereto Dr. Helen MacMurchy, a medical woman whose name has long been familiar in connexion with the study of questions relating to infant mortality, and who is personally known to many of her colleagues in this country owing to her attendance at the annual meeting of the Association in 1910. She will also bear the title of inspector of hospitals and public charities, and act in this capacity as assistant to the head of the hospitals department at the Ontario Home Office, Dr. Bruce Smith.

Address ON HEREDITY.

DELIVERED AT THE SEVENTEENTH INTERNATIONAL CONGRESS OF MEDICINE.

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

LET me on behalf of my colleagues, the students of genetics, express our deep sense of the honour conferred upon us by the organization of your Congress in choosing our science 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 exceptional significance that the study of heredity must before long assume, it would be mere affectation were I to suggest any misgiving as to the propriety of allotting to this subject a conspicuous 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 he drew from a broad contemplation of the facts of descent. Traces of order among these phenomena he did indeed perceive, and by great labour and ingenuity he even gave numerical expression to his conclusions. But great as his services were in attracting attention to the problem, no one before the re-discovery of Mendel's work had ventured to imagine that the confusion, the paradoxes, the capricious disorder of the phenomena of descent were, in very great measure, capable of a simple and ready analysis. It is this knowledge which has given to genetic science a position paramount among the branches of physiology, showing that in accurate genetic analysis a means is given not merely of elucidating the inter-relations of parent and offspring—the immediate subject of our investigations—but of contributing also to a right interpretation of various special problems of pathology and of anthropology, perhaps, also, to a true understanding of the course of human history; and certainly to the direction and control of the destinies of mankind. Knowing, as I must, that the manner in which these issues are presented to you to-day cannot fail to influence in some measure the development of genetic study in the medical world, I should be insensitive did I not feel how responsible is the position I now occupy. Most of all I fear that I may seem in some degree to exaggerate not the importance of the principles already ascertained, but the precision with which they can be shown to apply in the special cases of human physiology. In all the arts, perhaps most in the art of exposition, the hardest thing is to simplify the presentation by the omission of detail, and at the same time to leave the picture true to natural fact. So let me, therefore, at the outset say that in regard to almost every instance of principle I shall bring before you, though rule may be perceived, we have evidence of exceptions also. This is true even of the rules traced by minute analysis in the plants and animals amenable to experiment, and necessarily far more true of the human phenomena which are brought within our reach for the most part by imperfect records. As in every department of physiological advance, we have first to trace the course of those great sweeping curves which lead to the recognition of ascertained law, and later those minor deviations, perhaps equally significant, which must hereafter be the subject of a further analysis.

Now the essence of Mendelian principle is very easily expressed. It is, first, that in great measure the properties of organisms are due to the presence of distinct, detachable elements, separately transmitted in heredity; and secondly, that the parent cannot pass on to offspring an element—and consequently the corresponding property—which it does not itself possess. The determination or recognition of these elements by analytical breeding is one of the main objects of present-day genetic research. Each germ cell, ovum or sperm, may contain or be devoid of any of these