the first page Mr. Hale modestly states, "among the results of the year's work the following may be mentioned," and then he follows this with brief paragraphs, *thirty-five* in number, each of which is a piece of valuable research work far-reaching in its aim and an important thread in the web which comprises the complete knowledge of stellar distribution and development. Some of the results of these researches have been published in *The Astrophysical Journal*, and received notice in our astronomical column.

The past year has marked the completion of the 150-ft. tower telescope, and great things are expected of it in the future. The work so far done with it has proved that it is perfectly stable and on no occasion has trembling of the image been recorded. It may be mentioned here, and it is not generally understood, that the girder work forming the visible tower is really in duplicate, each girder containing another one inside completely independent of it, and not touching it, and thus forming a complete second but invisible tower. The outside girder work is thus designed to protect the inner one from vibration caused by the wind. The cœlostat and secondary mirror placed at the top of the tower are fixed to a

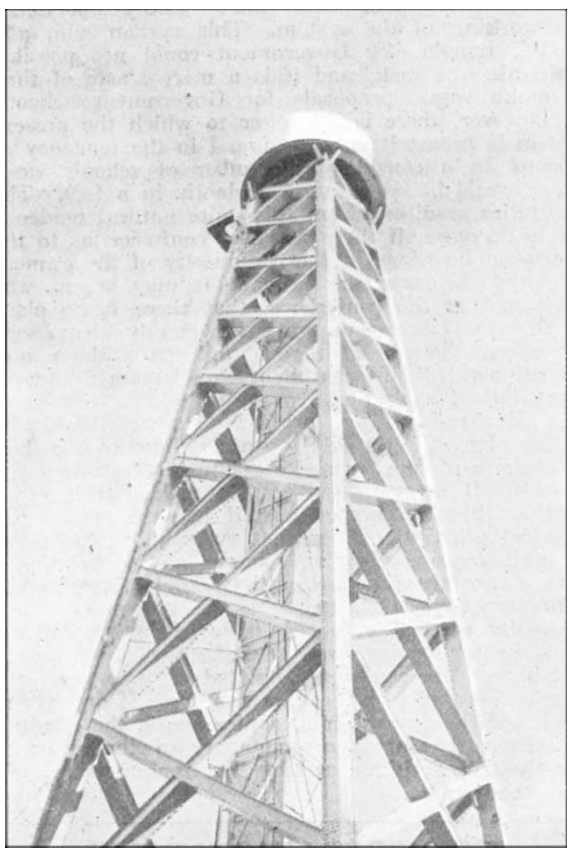


FIG. 1.—The tower telescope as seen from immediately below, showing the platform and dome at the top.

platform resting on the inner tower. The definition of the solar image is stated to be better than that of the Snow telescope after the early morning hours in consequence of the protection of the beam. In our astronomical column for March 20 a statement was quoted from *The Observatory* for March that the 100-in. mirror, when tested, was found to be probably useless. Mr. Hale, in his report, states that the tests indicate that it may become necessary to discard the disc, but in a footnote adds that "since the above was written. . . . There is now every reason to believe that the present mirror will prove suitable for use in the telescope." It may be that the information in *The Observatory* refers to a further examination subsequent to the footnote. The 60-in. reflector has a very large programme of work allotted

FIG. 2.—The observing house is directly below the tower and above the spectroscopes, which are situated in a deep vertical pit in the mountain.

to it, and mention is made that Prof. Barnard would prefer it for visual work on the planets to any of the large refracting telescopes with which he is familiar. This report will be a revelation to those who work at astrophysics or solar physics this side of the Atlantic, and will probably make some workers very downhearted when they compare their own means of research with those available at Mount Wilson.

CHEMIO-THERAPY.[1]

IT must be a great pleasure and a special honour for all of us to meet here personally 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 public plague as smallpox, still shines with peerless splendour. And on the occasion of the last congress which 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 medicine. Here in England the first example of a modern Institute for Tropical Diseases, which is a model for

[1] From an address delivered before the seventeenth International Congress of Medicine at London on Friday, August 8, by Prof. Paul Ehrlich.

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 causes of malaria was so far advanced that entirely new lines were opened up for the hygienic struggle against tropical and subtropical diseases.

The proof by Castellani that a trypanosome is the cause of 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 the cases of trypanosome diseases was first established in the Liverpool Tropical Institute by Thomas and Breinl, and quite recently Plimmer has brought forward the use of tartar emetic as an effective weapon against protozoal diseases.

The life-work of Almroth Wright is also known to all of us, *i.e.* his work on opsonins and on the prophylactic treatment of typhoid fever, which has been carried out in a practical and most excellent 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 diseases was at all times the highest aim of medical aspirations; however, a systematic pursuit of this purpose has only been possible in recent times, as through the labours of all civilised nations we have got an insight into the nature of infections, the cause of diseases, and the means by which they are transmitted. Through these methods it has been possible to infect animals artificially and so obtain material on which to test the drugs in a systematic and rational manner. From the very first beginnings of therapeutics, chemio-therapy has indeed been in existence, as all the remedies which we employ are chemicals; on the other hand, experimental chemio-therapy 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 the chemio-therapeutic work. 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 chemio-therapy 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. So, 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 iodide of potassium 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 chemio-therapy not to build on the basis of exceptional work, but it is better 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 parasiticides, 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 anti-substances. This view is based mainly upon the fact that if one mixes the substances in question, such as, for instance, neosalvarsan, with certain pathogenic agents, *e.g.* spirochætes, 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 Prof. Hata, the conclusion has been drawn that salvarsan or neosalvarsan, as such, did not in any way directly influence the spirochætes. Now it can very easily be shown that this conclusion is quite incorrect. If, for instance, following Castelli, one suspends the spirochætes 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 neosalvarsan, and if one then centrifugalises and then draws off the liquid; if one washes the remaining spirochætes again in a mixture of serum and again centrifugalises it; then one obtains in both tubes a deposit of spirochætes which on microscopic examination shows the same properties, *i.e.* equally good mobility of the spirochætes. If, however, the spirochætes obtained in this manner are injected into test mice, then one can very soon convince oneself that the spirilla treated with salvarsan do not give any infection to the animal, whilst the mice vaccinated with the contents of the control tube promptly shows signs of infection. This proves that salvarsan or neosalvarsan, as the case may be, is absorbed by the spirochætes, 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 increase of the parasites in the animal body. Therefore, by this very simple and easily intelligible experiment, the direct effect of salvarsan and neosalvarsan on the spirochætes, and thereby the principle of fixation, is absolutely proved; the objection of the indirect effect based upon anti-substances therefore falls to the ground.

It was necessary, however, to penetrate more deeply into the mechanism of this fixation of remedies, and it is only after long-continued efforts that success has been attained in obtaining a clear conception. In order to make practical progress it appeared to be necessary not to be satisfied with the primordial idea, but to see in what manner the drugs are fixed by the parasites, or, as the case may be, by the cells. Only by taking a very roundabout way has it been possible to obtain clearness with respect to these complicated relations, and in this connection it was especially the studies on trypanosomes and especially the investigations of "drug-fast" strains of germs, which led to quite definite representations with regard to the process of fixation. There was no difficulty by continued treatment of the experimental mice with certain definite remedies, *e.g.* fuchsin, in finally obtaining a race of trypanosomes which had become immune against these remedies, *i.e.* "drug-fast," in the case mentioned above immune to fuchsin. There were especially three classes of different remedies which were very suited to this purpose:—

(1) The class of the arsenic compounds, in the following historical order: arsenious acid, arsenilic acid (atoxyl), arsenophenylglycine (salvarsan and neosalvarsan).

(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, &c.).

When a race of trypanosomes has been rendered

immune against fuchsin, then this race is immune against all the allies of fuchsin and methyl violet, &c., but it is not immune against the two other classes.

Also a race immune against arsenic compounds is only immune against such, but not against 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, *i.e.* those relating to toxins and antitoxins, pointed to the nature of the said processes. In connection with these 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 characterised as "receptors," and that the anti-substances 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 about transferring these views relating to receptors to chemical bodies at all, and in this connection 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 chemo-receptors seem probable to me.

From this point of view, the phenomena observed in connection with the "drug-fast" strain of germs can be readily explained experimentally, owing to the fact that the chemo-receptors 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, *e.g.* of a race of arsenic-fast trypanosomes, 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 chemo-receptors,* for instance, the *arseno-receptor,* which fixes the trivalent group of arsenic as such; and the *acetico-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 chemo-receptors of a certain definite parasite is what I should like to characterise as the *therapeutic physiology of the parasite cell,* and this is a *sine quâ non* of any successful chemio-therapeutic treatment. I should like to emphasise the fact that many observations indicate that certain chemo-receptors 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 chemo-receptors, therefore, which can be demonstrated the greater is the possibility of a successful chemio-therapy.*

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 chemo-receptors 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 and only a few are capable of bringing about its destruction.

In the therapeutically suitable substance there must, therefore, in addition to the fixing group, which brings about the fixation of the *haptophorae,* be another, which as such brings about the destruction, and therefore is to be characterised as the "poisoning" or *toxophoric.* This representation exactly corresponds to the views which we have already long since obtained 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 as separate groups are linked with a chemical molecule in the character of side-chains. In this way we arrive in a natural manner to this, that chemio-therapeutic 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 chemo-receptor of the parasite corresponds to the point of the arrow, the binding member is the shaft, and the poison group is the arrow poison fixed to the shaft of the arrow. Corresponding to this scheme in the case of salvarsan (dioxydiamidoarsenobenzol) the benzol group would correspond to the shaft, the ortho-amidophenol group to the point, and the trivalent arsenic group would correspond to the toxophoric group.

If we continue this comparison, then the substances which are used for poisoning the arrows are alkaloids and similar substances, which act injuriously on certain definite vital organs of the body; and so we shall also have to assume that the toxophoric grouping of the synthetic drugs poisons 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, *i.e.* in the fully saturated form, do not bring about any therapeutic action, but that this only commences when the arsenic group exists in the unsaturated condition corresponding to the trivalent radical, certainly points in the same direction. This difference between the saturated and unsaturated arsenic radical 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 the subsequent period a very large series of analogous cases have become known corresponding to this truth, which point to the increased effectivity of the unsaturated radical. The best-known example is doubtless the high degree of toxic power of carbon monoxide as compared with the almost indifferent carbon dioxide.

Dyes act as bactericides only as such, but not in the form of their colourless products which correspond to the saturated type. *The fact is that all these unsaturated combinations contain unsatisfied avidities which render them capable of reacting additionally with other combinations.*

If, therefore, we poison a spirochæta 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 to exert its toxic effect. The avidity of the arseno-receptor can in itself be such that it can only react if favouring

factors, which chemically must be regarded as a stereo-chemical facilitation, come into action.

Examples of such stereo-chemical facilitations are frequently found in chemistry, *e.g.* in the chemistry of the ortho-condensations. And so the haptophoric group of the arsenic molecule primarily brings the arsenic along to the cell, and secondarily brings about its possibility of action.

Now, it is a frequent practice of many uncivilised peoples, in order to be certain of killing their enemies, that they not only rub over their arrow with one kind of poison but with two or three totally different kinds of poison. And so it also appeared advisable to imitate this procedure against the parasites, which is otherwise not very praiseworthy, and to poison our synthetically poisoned arrows not singly but doubly. In association with Dr. Karrer I succeeded in depositing the reduced arsenic compound, *e.g.* salvarsan, even on metals, and so in arriving at remedies which, used experimentally on animals, show an increased effect.

In the previous remarks I have described the conditions which are necessary in order that a certain substance may exert a parasiticidal effect, and indeed must effect such, if it operates directly on certain definite parasites in an aqueous solution, such as, for instance, is the case with the ordinary disinfectants. In the manner described above it is easily possible to arrive at 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 is set before us of sterilising a room, then indeed it is an easy matter 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 bring about a colossal bactericidal effect in aqueous solutions even when they are highly diluted, 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 parasitotropic and organotropic as to 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 even 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 organotropic to parasitotropic 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 generally the case.

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 in infinitesimal quantities by the parasites. According to a biogenetic foundation principle it is quite a common thing for substances which act destructively in *large* quantities to bring about an *increase in the vital functions* in smaller doses. Only such substances, therefore, can be used as therapeutic agents in which the ratio between organotropic effect and parasitotropic effect is a favourable one, and that can be easily ascertained by experiment by a comparison between *dosis toxica* and *dosis tolerata*. *Only such substances can be considered therapeutic agents 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 chemo-receptors, 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 vital colouring.

I will mention here—in order only to indicate a few examples—the methyl blue colouring of the nerve trunks, the neutral red colouring of the cell granules, and the distribution of the isamine 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 papillæ 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 pyronine series in the case of mice brings about a general dropsy amounting to 50–60 per cent. of the body without injuring the kidney, which 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 connections of a specific nature must take place, which must be referred to the presence of certain definite chemo-receptors.

Now, according to the above representations, all these fixations are dependent on the haptophoric grouping of the drugs, and, therefore, it was a matter of great interest to observe how phenylarsenic acid, the mother-substance of the modern arsenic compounds, behaves when various different groups are attached thereto. In this connection it has turned out that when we introduce different constituent fixation groups, *e.g.* chlorine, the oxygen group, the hydrocyanic acid group, the sulphuric acid group, the ammonia radical, we can manufacture, starting out from one substance, a series of combinations, the toxic effect of which may vary fifteen hundredfold. The combinations which are to the greatest extent free from poison—these are derivatives of sulphuric acid, especially the sulpho-phenylarsine acid and its salts—are less toxic than sodium chloride, and, on the other hand, there are substances the very smallest quantity of which brings about death. And in this connection 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 diarrhœa; 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 anæmia. Frequently also the central nervous system becomes injured, and in the case of mice this usually relates to the vestibular nerve of the inner 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

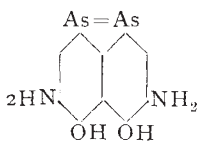
phenylarsine acid. The cases of blindness which have been observed after the use of very large doses of atoxyl, arsazetin, and other drugs are due to this injury.

From this it is evident that according to the selection of the group annexed to the phenylarsine acid quite different organs will be affected. This is only explained according to the above views by the fact that there are, as already previously stated, in the various organs specific chemo-receptors which energetically attract certain fixation groups somewhat as the 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 phenylarsine acid group, or, as the case may be, to the phenylarsenobenzol group, such grouping as is only related in a small degree to the organs of the sick body, but, on the other hand, is very closely allied to the receptors of the parasites.

I have explained above that the parasites possess a whole series of chemo-receptors 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 if we select a haptophoric group which is especially adjusted to the functions of the parasites:

A remedy provided with such a haptophoric group would be entirely innocuous in itself, as it is not fixed by the organs; it would, however, strike the parasites with full intensity, and in this sense it would correspond to the immune productions, the anti-substances discovered by Behring, which, after the manner of the bewitched balls, fly in search of the enemy. Let us hope that it will be possible chemio-therapeutically 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 sicknesses, *e.g.* spirillosis in hens, 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 nil dose, 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. Among the numerous combinations which have been tested in experiments on animals in the case of trypanosomes and spirillar infection, and in the preparation of which I have been supported by the untiring co-operation of Dr. Benda, Dr. Bertheim, Dr. Kahn, and Dr. Karrer, and which have been biologically tested, especially by my respected friend Prof. Hata, and later by Dr. Castelli and Dr. Gonder and Frl. Leupold, salvarsan has proved to be the most efficient, the dioxydiamidoarsenobenzol of the formula.



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

But now, gentlemen, the step from the laboratory to practice, *i.e.* 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; (2) it has been shown that certain illnesses of a constitutional nature can cause a supersensibility.

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

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 remedy is applicable: "Frapper fort et frapper vite."

We have to ask ourselves the question, What are the causes which make it possible for 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 assisting 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., and 5 per cent. have resisted its action, then these remaining 5 per cent. are sure to 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 minimised considerably owing to the biological properties of the parasites. For it may happen that a part 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 known as a relapsing crop. It is clear that parasites of this kind which are able to form a large number of relapsing crops offer very great difficulties in their treatment, as in this case 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, as owing to their great power of adaptation a single germ surviving may perhaps be the cause of the infection breaking out afresh.

If we compare the fight against parasitic diseases with a state of warfare, we find that, on 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 sterilisata.* If, on the other hand, a fortress has to be taken, the goal cannot be reached with one single stroke, but it may take months and even years.

The measures employed in connection with a bacteriological siege aim on the whole at rendering the places which are not easily accessible more accessible for the therapeutic agent than is the case under 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 chemo-receptors

in the parasites. For instance, it is useless to combine euchsin with its nearest relative, methylviolet; and it is useless to combine therapeutically trypane blue and trypane 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."

Combined therapy will in the future conquer an ever-increasing field of action. Thus, for instance, Broden, in the Congo, succeeded in connection with sleeping sickness in the human subject—it is true only in the early stage of this infection, which is so difficult to fight against—in obtaining good results by the combination of salvarsan and two basic colouring matters (trypallavin and tryparosan) by treatment lasting about a week.

It is precisely in the manifold character of the possibilities of combination that I see a special advantage, and peculiar possibilities of development. When once we are acquainted with the majority of the chemoreceptors of a particular kind of parasite, which will be a long piece of work, occupying many hands and heads, we shall have the most far-reaching possibilities of simultaneous attack by various agencies. And on this account combination therapeutics are also absolutely pluralistic in contrast to antitoxins, 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 also caused by spirochætes, and is a scourge of the tropics, curing 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 more than 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 the patients could all be discharged but two. It is to be hoped that in this way it will be possible altogether to extirpate framboesia.

Exactly the same favourable results have been attained with recurring fever in the human subject, the fever immediately subsidising after the injection of salvarsan, and the patients being cured by one injection. The very rare cases of relapse occasionally occurring 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, which are caused by spirochætes of the mouth, *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 which form, but in this form alone, salvarsan has proved successful, and blastomycosis (Petersen) and the Aleppo boil. As regards diseases of animals which can be cured by one 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 emetin to be a specific against the very serious amœbic 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* or *sterilisans fractionata* is employed, provided only he is relieved of his sufferings in a harmless manner.

Piroplasmosis also, which exerts a disastrous action, causing serious diseases in cattle and dogs, may, according to the observations of Nuttall, be favourably influenced by a pigment belonging to the class of trypane colouring matters, viz. by trypane blue, which was first composed 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 save their valuable animals scot-free from this serious disease.

It is indeed easy to understand that the schizomycetes, which in themselves are so much hardier than the tender protozoa and spirochætes, 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 ethylhydrocuprin.) But in the case of hardier bacteria, too, such as the *Bacillus typhosus*, the possibility of sterilisation 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 on this species of animal.

If I briefly allude to the very hopeful experiments of Gräfin 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 recognise 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 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, Gafftey, Pfeiffer, in the first order, 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, which is connected with the name of Theobald Smith, and has led to the most important consequences.

On the other hand we have the study of the immunity theory which was first inaugurated so bril-

liantly by Metchnikoff, and received a new impetus from the wonderful discovery of antitoxin by von Behring, through which a wide new field, that of the science of immunity and the investigation of serums, was opened up, on which 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 diagnosis and therapeutics cannot be estimated.

All these discoveries, especially in regard to the ways of spreading diseases on the part of the infecting agencies, 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 been able to derive advantages from these discoveries, the most wonderful example being the diphtheria serum.

Now that the liability to, and danger of, disease are to a great extent circumscribed, so far as epidemics and many other diseases are concerned, the efforts of chemio-therapeutics are directed so far as possible to fill up the gaps left in this ring, more especially to bring healing to diseases in which the natural powers of the organism are insufficient. And I believe that now when definite and sure foundations have been laid for the scientific principles and the method of chemiotherapeutics, the way is visible before us; not always an easy but yet a practicable way. In the diseases involving protozoa and spirilla extraordinarily favourable results, as I have shown, have already been gained, which can also satisfy far-reaching tests. There are many valuable indications that in a series of other diseases—smallpox, scarlatina, typhus exanthematicus, perhaps also yellow fever, and, above all, infectious diseases caused by invisible germs—the prospects of success are brightening. But in contradistinction to these super-parasites the ordinary or common bacterial diseases (diseases due to the streptococcus and the staphylococcus, coli, typhoid, and dysentery, but, above all, tuberculosis) will still require a hard struggle. Nevertheless, I look forward with full confidence to this development also, and might, without being set down as an optimist, 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 are taken into consideration in a struggle with diseases, 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 very best materials for fighting the diseases, or 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 rise with the number of those who occupy themselves with the definite problem. It is just at this point, above all, that necessity arises to gather and unite all powers, and here special force attaches to that motto, *Viribus unitis*, which gives guidance in so many other fields; which in so exemplary and fine a way is the foundation of this great International Congress, to which thousands have been drawn from all lands, to give their testimony that in the world of science all national barriers have disappeared.

UNIVERSITY AND EDUCATIONAL INTELLIGENCE.

LEEDS.—The council of the University has accepted with deep regret the resignation of Mr. Roberts Beaumont, professor of textile industries. To mark its sense of the value to the University of his work, extending over a period of thirty-four years, the council has placed on record its high appreciation of the services which, during his long tenure of the professorship, Prof. Beaumont has rendered to the cloth-workers' departments of the University, and to technical instruction in the textile industries.

LONDON.—Dr. W. C. McC. Lewis, having been appointed to the chair of physical chemistry in the University of Liverpool, has resigned his office in connection with the department of chemistry at University College. Dr. R. E. Slade has been elected to succeed him as assistant. Dr. Slade was educated in the University of Manchester. In 1909, he was appointed assistant-lecturer in physical and electrochemistry at the University of Liverpool, and was subsequently appointed lecturer-in-charge of the department of physical chemistry.

Dr. A. J. Clark, assistant in the department of pharmacology at University College, has been appointed lecturer in pharmacology at Guy's Hospital Medical School. His successor at University College will be appointed at the beginning of next session.

THE short Education Bill recently introduced into the House of Commons by the President of the Board of Education, which dealt with grants in aid of building, has been dropped for this session, owing to the great pressure of Parliamentary business.

BY the will of the Rev. L. C. Chamberlain, we learn from *Science*, 5000*l*. is bequeathed to the Smithsonian Institution for its mineralogical collections, and 2000*l*. for its collection of molluscs. There was also bequeathed 1000*l*. to the Academy of Natural Sciences in Philadelphia for increasing and maintaining the Isaac Lea collection of Eocene fossils. These bequests were made for the benefit of the scientific work in which the late Mr. Isaac Lea was interested, Mrs. Chamberlain, his daughter, having inherited the money from him. Mr. Chamberlain also bequeathed 20,000*l*. and his residual estate to the Thessalonica Agricultural and Industrial Institute, Turkey.

THE programme for the session 1913–14 of the department of technology of the City and Guilds of London Institute has now been published by Mr. John Murray. It contains the regulations for the registration, conduct, and inspection of classes, for the examination of candidates in technological subjects, and for the award of teachers' certificates in manual training and domestic subjects. The regulations are in the main the same as those of last year, but the rules respecting the award of full technological certificates have been revised. The passing of examinations in science, and in some cases in art, held by approved schools will be accepted as a qualification for the full certificate. Under certain conditions, candidates from approved schools may be exempted from the examination in the first grade in some subjects in which the examinations are held in more than two grades. In a number of technological subjects the syllabuses have been rearranged and redrafted.

THE Illuminating Engineering Society has issued a preliminary report of the joint committee appointed in 1911 to consider the questions in connection with the artificial lighting of schools. The report appears in *The Illuminating Engineer* for July. The com-