The Annual Oration

ON THE TREND OF THOUGHT IN RECENT PHARMACOLOGICAL RESEARCH.

DELIVERED BEFORE THE MEDICAL SOCIETY OF LONDON.

BY

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PRESIDENT AND GENTLEMEN,—My first duty is to express my thanks for the high honour conferred upon me by the Medical Society of London appointing me Orator for 1913. I feel quite overwhelmed when I reflect that with hosts of metropolitans of world-wide fame, all far better fitted to fill this exalted position, you have honoured the outpost of civilization to which I belong by selecting an obscure provincial to address you to-night.

My colleagues and professional brethren across the Channel cling to the belief that though separated by this turbulent streak of melancholy ocean they are as proud of the traditions of English medicine as if a bountiful Providence had cast their lot in the heart of your mighty metropolis on the banks of the Thames instead of on the quiet shores of the Lagan. Therefore, though it may not be permitted of me to refer in these degenerate days to loyalty of a different kind, I nevertheless rejoice in assuring you that our pulses throb in unison with your own in every aspiration for the advance of British medicine.

In casting my eye over the wide domains of the science and practice of our art in search of a subject to claim your attention for a brief hour to-night the present condition of the field of therapeutics suggested itself. In no other department of medicine at the moment is such laborious research manifest or have there ever been more earnest attempts made to utilize every discovery in other branches of science for the prevention of suffering and for the relief and cure of disease. The triumphs of physics and the advances of synthetic chemistry are being daily pressed into the service of therapeutics, and each addition to our knowledge in pathology, etiology, and diagnosis is valued by the standard of how far it shall be found useful in leading up to a more successful treatment of human maladies. The result of this ceaseless activity has been an advance in the art of healing during the last three or four decades, which is perhaps as great as the progress registered in any corresponding number of centuries.

Whilst the militant army of chemists, bacteriologists, and pathologists was successfully wresting from Nature her treasured secrets when the majority of my present auditors were entering upon their professional studies, the therapeutic battalion seemed to be merely marking time. These were the days when the pessimist and the sceptic, strengthened by the startling revelations of microscopic changes in diseased tissues, and emboldened by the failures of empirics or the visionary seekers after specifics, scoffed loudest at the bare possibility of such results as have been since achieved. This condition of affairs was not without its depressing and retarding effect upon therapeutic progress, so that even the facts accumulated throughout many years of patient clinical observation on the old and well-tried remedies were frequently denied or altogether ignored, because a scientific explanation of their action was not immediately forthcoming.

In the present age of pharmacological activity and discovery, when the air is still ringing with the marvellous results achieved by such agents as thyroid extract, diphtheritic antitoxin, and salvarsan, we have to guard ourselves against the allurements of the opposite evil of credulity. We can, however, always rejoice in the existence amongst us of the honest doubter—one of the best assets of British medicine—for only through honest doubt can we hope to reach the final goal of sure belief—the essential factor in successful therapy.

The present seems to me, therefore, a suitable opportunity for pausing and investigating the truth of the more important theories which, like beacon lights, have been guiding pharmacologists in their successful search after new remedial agents. Obviously, the brilliant triumphs achieved by operative surgery and Listerism cannot come under our immediate consideration, owing to the shortness of the time at my disposal; neither, indeed, is it necessary to speak of them, since they have been ably dealt with by more than one of your recent annual orators.

On the threshold of such an inquiry we are reminded that very often the advances made in one era are to be traced backwards to their origin in a rational or accidental discovery made at a much earlier date, and sometimes to a research the importance of which was overlooked at the time. Should such a retrospect in the domain of therapeutics prove successful in elucidating a scientific starting point to which our present advances can be reasonably attributed, the subject becomes of more than a mere historical or academical interest, since we can confidently hope for further progress so long as research is conducted upon the lines originally laid down, or lines directly or indirectly communicating with the main track.

Such a starting point, I believe, may be found in the epoch-making researches on the action of methylstrychnine, conducted by Crum Brown and Fraser in 1868. It was well known that ammonia and its derivatives, when administered to animals, caused stimulation of the spinal cord and medulla, which ended in convulsions; it was also recognized that the chemical constitution of the vegetable alkaloids corresponded to the type of an ammonia derivative. These experimentalists made the discovery that by linking the organic alkyl radical, methyl (CH_3), to the nitrogen of the complex molecule of strychnine, the resulting comparatively slight change in chemical structure altered in a remarkable manner the physiological or pharmacological action of the alkaloid. The alteration was manifested by a change from the convulsant effect on the cells of the cord to a paralytic one on the terminals of the motor nerves, such as is witnessed in the well-known symptoms of poisoning by curare. This change of physiological action being manifestly due to the transformation of the original tertiary base into a quaternary ammonium compound, it was not to be wondered at that almost identical results were obtained by altering in the same way the chemical constitution or structure of a number of the other alkaloids exercising widely different actions on the human body.

Similar change in physiological action is also obtainable by linking other alkyl radicals, as C_2H_5 instead of CH_3 , the radicals being, in each case, previously combined with iodine or bromine. That this change in action is not a mere coincidence or accident, is demonstrable in a remarkable manner by the methylation of curare itself—the drug which, in its natural state, affords the most typical example of a paralytic effect upon the motor nerve endings. This substance contains two ammonia bases—the active curarine and the comparatively inert curine. Now, if the latter base be altered by the before-mentioned manipulation with methyl, the transformation in its chemical constitution causes it to become about 230 times more poisonous than before, and the resulting new compound is found to be identical with curarine, the active principle of the drug.

Sir Lauder Brunton, to whom British therapy owes so much, speaking in 1886 of Crum Brown and Fraser's discovery as directing pharmacological advance along a new path, prophesied that another twenty years would not only add greatly to our stock of remedial agents, but to a better knowledge of our patient's condition, ushering in the era when we should be able to ensure the drug action we desired without feeling that our patients often died for lack of knowledge, not on our part but on that of our art. We all feel painfully that such a millennium is still far off, but, nevertheless, we are steadily, if slowly, approaching it. If we interpret Brunton's forecast concerning "our better knowledge of the patient's condition" as implying a clearer conception of the incessant changes taking place in the protoplasm of the body cells, it must be conceded that enormous strides have been made in our progress in this direction, since, during the last quarter

of a century, a chemical basis has been industriously constructed, upon which the science of pathology now securely rests—a fact not sufficiently recognized, even by pharmacologists.

Therefore in a re-survey of our therapeutic position any examination of the value of the theory concerning the relationship between pharmacological action and chemical constitution must proceed hand in hand with a consideration of the advances made in chemical pathology and physiological chemistry. The truth of the axiom that pathology must constitute the basis of every rational system of therapeutics is more obvious to-day than it was fifty years ago, at which time the study of diseased processes was mainly conducted on morphological lines. If the science of pharmacology is to rest upon the arch of pathology, whose keystone is physiological chemistry, it obviously follows that this foundation must be sufficiently strong and wide to support the growing fabric of all scientific therapy.

The subject of the relationship between physiological action and chemical structure is a most complex and tedious one for treatment in a solitary address, especially as the high pressure and whirl of professional activities permit few practitioners to cultivate the habit of thinking in chemical language. The nature of our work almost compels us to think out our clinical problems from the physical or vitalistic point of view, hence in my attempt to review the accumulating evidence in favour of accepting the doctrine of a close connexion between the action of a drug and its chemical structure I shall try to avoid as far as possible references to complicated graphic formulae and the highly technical phraseology of the student of organic chemistry.

It was expected by pharmacologists that Brown and Fraser's discovery would immediately revolutionize the science of therapeutics, but in this they had to realize soon a keen disappointment. The application of a few swiftly constructed generalizations to the solution of intricate therapeutic problems at first only led to failure and chaos, and, as always happens, a revolt against the new doctrine soon appeared. Even at the present hour some pharmacologists may be seen labouring under the old incubus of trying to explain the action of drugs on the theory of some purely physical or mechanical property in their atoms or molecules, whilst others are falling back hopelessly upon the ancient vitalistic conception. Hence arises the importance of a scrutiny of our present position, since the problem is not one to be decided only in the laboratory, but to be finally tested by the practitioner at the bedside.

It is hardly necessary to remind my auditors that in the examination of the theory of the relationship between pharmacological action and chemical constitution we must put aside the question of the mere chemical composition of a drug. It is not the number or nature of the atoms in a compound which we have to think of, but the plan of structure by which these are built up and linked to each other in the drug. In other words, it is not a consideration of the number or nature of the individual bricks or building stones employed, but the manner in which these are grouped together in the molecules of the compound radicals determining the final chemical construction or constitution of the compound. This vital distinction between the structure and composition of a chemical compound is seen in the empiric formula $C_6H_{12}O_4$, which is the label attached to no fewer than sixty-six compounds—all totally different substances. It is true that a simple change in the mere composition of a salt may change or vary greatly its action, but this will generally be found to be due to some alteration in its solubility which causes retardation of its absorption or acceleration of its elimination. Thus the victim of the malarial parasite can be often speedily rescued from his perilous toxæmia by a moderate dose of the hydrochloride of quinine when he would perish with an enormously larger amount of the insoluble alkaloid or its sulphate lying unabsorbed in his gastric cavity.

After the demonstration of the results of methylating the strychnine molecule came the valuable generalization of Brunton and Cash on the actions of the carbon compounds. These observers pointed out that the two great fundamental groups met with in organic chemistry differed very materially in their pharmacological actions. The

substances built up on the open-chain plan, the type of which is marsh gas (CH_4) and chloroform ($CHCl_3$), all paralyse the nerve centres and tend to exert an anaesthetic action, whilst the close chain or ring series, represented by the benzene nucleus, produce convulsions or spasms before paralyzing. Liebreich, seizing the truth of this common paralytic action of the open chain or fatty series of the carbon compounds, started out in search of a new hypnotic, which ended in the discovery of chloral, as Schmiedeberg likewise gave to therapy the invaluable hypnotic—paraldehyde.

When one of the hydrogen atoms in the closed benzene ring is replaced by the radical hydroxyl (HO) phenol is formed, and as each of the other hydrogen atoms is substituted by a further hydroxyl addition, or by methyl, the antiseptic power of the resulting aromatic compound proportionally increases. It was found that by varying the position of hydroxyl in the ring valuable antipyretic qualities could be developed; thus was achieved a notable triumph in therapeutics by advancing from hydroquinone to the synthetical building up of kairin, thallin, and finally of antipyrine.

Since then innumerable examples have accumulated equally suggestive of this close relationship, a mere recital of which would occupy the entire time at our disposal, and by their multiplicity would obscure the issues under consideration. It is noteworthy that these examples tell in opposite directions. Not only is the synthetical chemist able, by altering the structure of the molecule, to intensify greatly the action of the compound; but he can, with equal ease, render the poisonous drug inert by introducing into the molecule such acidic groups as the sulphuric, sulphonic, and carboxylic. Thus the poisonous phenol is converted into the inert phenyl-sulphuric acid, and morphine-sulphuric acid can be swallowed with impunity in drachm doses. Notwithstanding, however, these accumulating instances of close relationship, it must be conceded that it is still impossible for the pharmacologist to foreshadow with absolute certainty the physiological or therapeutical action of a particular untried drug, so that rational must proceed in company with a certain degree of empirical therapy. But the shrewd guesses of a couple of decades ago are now being replaced by the stronger probabilities of later years, and by the almost certainties of 1913. It is often argued by the sceptic, with an apparent show of reason, that this relationship between chemical structure and pharmacological effect, if it be a definite law, should always afford the certainty of a mathematically correct prophecy. That it does not is due to the fact of our want of knowledge about the construction of the molecules of the highly complex carbon compounds, whose number almost suggests infinity, and of which but a very few comparatively have been studied structurally. Each discovery of the true nature of the graphic formula of these shows that Nature is gradually, if reluctantly, yielding up her secrets to the indefatigable analytical and synthetical chemist, who at once seizes upon the advance as a new stepping stone from which to approach the creation of an entirely new compound with the almost certainty of obtaining a specific action upon some particular type of body cell or tissue. It is true that unforeseen secondary actions of the newly created drug may vitiate the desired result and prove a barrier to its safe use as a therapeutic agent, but often a further study of its complex molecule suggests a new substitution process by which untoward effects can be eliminated after handing back the compound from the pharmacologist to the synthetical chemist. Another real difficulty in the acceptance of the relationship as a definite law is the operation of the incessant changes, chemical and physical, which are occurring in the blood and body cells, but this difficulty, as already mentioned, is steadily being lessened by the new flood of light thrown on metabolic processes by the physiological chemist.

The few pharmacologists who attempt to belittle the importance or deny the truth of the intimate relationship between drug action and chemical structure because of their adherence to a purely physical or mechanical theory of the *modus operandi* of remedial compounds, appear to have overlooked the obvious possibility of the physical character of the molecules being entirely due to the chemical structure of their constituent groups. Thus, it cannot be too clearly realized that should some startling

discovery prove the correctness of the old physical theory (though such an event is almost inconceivable), the importance of the relationship as a factor in therapeutic advance would in no way be lessened, especially as it is abundantly recognised that the operation of purely physical laws plays an important part in at least either retarding or facilitating the entrance of the drug to the cells of the tissue upon which it acts.

Let us now, for a moment, suppose that sufficient instances are not yet forthcoming to justify us in regarding the connexion between chemical constitution and physiological action as a definite "law," but only as a working hypothesis, and let us glance at the results which have accrued to practical therapeutics from its application. No stronger proof could be produced for the demonstration of a truth in medicine or in any other science than the long list of new synthetic antiseptics, antipyretics, analgesics, local anaesthetics, and hypnotics, the discovery or creation of which has owed its origin not to empiricism, but to the inspiration of a rational therapy founded on the theory of this relationship. Truly men do not gather grapes of thorns or figs of thistles. If we even set aside the entire series of new remedial agents just mentioned, salvarsan would alone demonstrate the truth of the contention. Ehrlich in the introduction to *The Experimental Chemiotherapy of the Spirilloses* states that from the beginning of his medical studies he became possessed with the conviction that "if a connexion between the constitution and the physiological action were granted, this must be pushed further and the tissues must also participate in the distribution, and whereas formerly the substances were offered to the medical man by the chemist for testing purposes, the conditions could now be reversed and the chemiotherapist could give the chemist points which lead to the desired recovery of genuine curative substances."

To my mind the question of whether or not Ehrlich has discovered a genuine cure for syphilis sinks into insignificance when contrasted with the importance of the fact that his methods are based upon such a rock-bed of truth as must ultimately revolutionize the treatment of all parasitic diseases by chemical agents. That no single step in his laborious search for a remedy against the spirochaete was taken empirically or at haphazard is evident from his repeated assertion that from start to finish every advance was made in a most purposive manner and only after an exhaustive study of the molecular construction of each of his 606 tested compounds. How far Ehrlich pushed his conviction beyond the theory of mere relationship brings me to the consideration of the second great fundamental principle underlying the conception of a purely chemical basis for all therapy.

His term "chemiotherapy" implies a great deal more than the acceptance of an established dependence of action on chemical constitution. With this new word another working hypothesis leaps into view, and it is essentially different from the one which we have been considering. The mixing up of these two theories has already threatened a check to therapeutic advance. Stated in its most advanced form, this second theory attempts to explain the action of a drug as the result of a chemical combination of some of its groups with other constituent groups or radicals in the complex molecule of the living protoplasm of the cell or tissue upon which it acts. It must be at once conceded that such chemical reaction can only be proven in a few cases, and therefore cannot be said to rest, as a theory, on the solid basis which must be acknowledged as existing in the case of the established relationship between structure and drug action. Hence it is not surprising to find that some pharmacologists who regard the relationship theory as not incompatible with the older hypotheses of vital, physical, and catalytic actions, nevertheless deny the truth or probability of the newer doctrine.

It will repay us to put this working hypothesis of chemical reaction to the same severe test as we have applied to the outcome of Brown and Fraser's discovery in order to examine and determine what part it has played or is playing in therapeutic progress, so that we may judge of its truth by the fruit which it has brought forth. And here let me remind you that the molecular theory upon which the science of chemistry is based is still but a working hypothesis, and probably must remain as such

for all time. It has long been known that many drugs suffer a fundamental change between the periods of their absorption and final elimination from the body. The direction of this change, as put by May, is usually in the direction of a transformation of an active or poisonous substance into a less harmful compound, and though it cannot be accepted as proof that the effect of the original drug is due to a chemical reaction between its molecules and those of the living protoplasm on which it acts, it may nevertheless be incidentally mentioned that this knowledge has been put to practical account by suggesting to the synthetic chemist the planning of a new compound on the same type as the transformed eliminated product. In this way, from a study of the behaviour of aniline in the body, phenacetin and other valuable para-amino-phenol derivatives have been added to the therapeutic armamentarium.

The great difficulty of demonstrating the doctrine of a purely chemical basis for pharmacological action rests in our incomplete knowledge of the chemical construction of the living cell protoplasm and of the physico-chemical processes incessantly occurring therein. The puzzling and highly complex constitution of the proteid molecule is gradually being cleared up, and already about a score of its cleft off building stones have been examined and proved to be of definite chemical composition and constitution, containing strong basic and acid groups capable of combining with each other to form an infinite number of compounds. Though we are still a long way from a synthetical construction of a protein molecule, the building up of the polypeptides by Emil Fischer strongly encourages the hope that this giant achievement is a possibility in the not far distant future. How vast is the field for such research, and how numerous are the amino-acid groups all capable of combining with each other through their basic and acid radicals may be dimly appreciated by the estimation of the molecular weight of haemoglobin as 16,669.

On reflection it becomes obvious that the complexity of the construction of the molecule of the cell protoplasm and the almost infinity of its changing groups are in themselves arguments rather in favour of than against the theory of a true chemical reaction between the compound administered and some of the radical groups existing in the cytoplasm.

These considerations clear the way for a brief glance at Ehrlich's great side-chain hypothesis or working theory advanced in order to explain the phenomena of the action of the antitoxins of diphtheria and tetanus. It is based entirely upon the chemical conception, and at first view the remarkable fact is obvious that this purely chemical hypothesis was built up to explain the action of the most complex organic compounds known to science in order to elucidate the phenomena of immunization. It recognizes the fact that the toxin molecule contains a large number of complex organic groups or radicals bound together to a central chain or nucleus.

Some of these radical groupings possess a chemical affinity for other complex groups existing in the protoplasm of the cells susceptible to the poison. These chemical affinities constitute in the language of Ehrlich the side chains known as the anchoring group or haptophore, which combines with a receptor radical in the cell protoplasm, and thus fixes or anchors the toxin molecule to the protoplasmic molecule. The harmful radical in the toxin, being thus fastened in close relationship with a chemical group in the cell, combines with it through its toxophore radical, the chemical reaction accomplishing the injury or death of the cell.

According to this working hypothesis no result will follow the injection of a toxin unless the cells of the organism contain in their molecule a group or radical, known as the receptor, which possesses an affinity for the haptophore or anchoring radical in the toxin as well as a group capable of being injured by the toxophore side chain of the poison. The phenomenon of natural insusceptibility is thus easily explained, since the immune animal contains in its cellular protoplasm no receptors for the fixation of the toxin molecule. Of much more practical importance to the therapist is the working out of this hypothesis when applied to the elucidation of acquired insusceptibility or immunization, and of still greater importance is it in solving the problem of the action of

antitoxins in the cure of disease. When doses of the toxin short of producing a fatal result are injected the chemical reactions just described are assumed to have occurred, but the smaller amounts, instead of destroying the cell, only serve to excite it to regenerate its receptors. The cell is also further stimulated to produce more of the chemical receptor substance than is required merely to replace that which has already combined with the toxin, the excess being showered into the blood constituting the antibodies found in the serum. These, therefore, are to be considered as free cell receptors with unsaturated chemical affinities which immediately combine with the haptophore radicals of the toxin, thus effectually preventing them from anchoring to the cell protoplasm, without which fixation a toxic effect cannot be produced.

At the risk of wearying my auditors I have ventured to give this brief description of the side-chain hypothesis, which is often put in such technical language as to obscure its purely chemical application; we shall now glance rapidly at the practical results of serum therapy. This has been during the last few years confused often with vaccine therapy to the retardation of therapeutic advance. I have used the term "toxin" only in its now scientifically restricted sense as the poisonous product of a true secretion of a bacillus. It is necessary to keep in mind that probably only four pathogenic bacilli really secrete a chemical poison. These are the microbes of diphtheria and tetanus, botulismus and pyocyanus bacilli. The toxins obtainable from castor and croton seeds do not come within our present scope, and the product of Shiga's bacillus is still of doubtful nature. All the other vegetable parasites contain their poisons as an intracellular chemical or endotoxin, which can only operate deleteriously on the tissues after the death and dissolution of the microbe. This fact constitutes the fundamental difference between serum and vaccine therapy. Only toxins lead to the formation of true antibodies in the serum.

Sir Almroth Wright, who never loses an opportunity for demolishing the untenable pretensions of those who apply serum therapy to the treatment of bacterial diseases other than those of diphtheria and tetanus, speaks of the action of the serums for these latter affections as a miracle of successful immunization—a miracle which gives in a few cubic centimetres a sufficient antitoxin to change the entire course of the patient's disease. When we remember that Behring was able to immunize an animal to such a degree that one thousandth part of a single drop of its serum was sufficient to neutralize a lethal dose of the chemical toxin, we become able to realize that there is nothing in the whole realm of therapy which rests upon a more secure foundation than the serum treatment of diphtheria and tetanus. The comparative failure of the antitoxin of the latter disease only strengthens the structure upon which the therapy is erected, since by the time the first symptoms of trismus have appeared a chemical combination between the groups of the toxin and the molecule of the cell protoplasm has already taken place. We are even justified in asserting that if we could know the exact moment at which the bacilli of these diseases enter the body, by an immediate resort to the serum a fatal issue would always be averted.

It is necessary to realize the truth of this in order to judge rightly of the value of Ehrlich's hypothesis, which explains, on a purely chemical basis, almost every problem met with in the marvellous processes of active and passive immunization, notwithstanding the theoretical qualifying views of Arrhenius and Madsen regarding dissociation, or the adsorption theory of Bordet and Biltz and the recent experiments of Abderhalden with the polariscope. But even if we assume that the side-chain hypothesis does not assist us in establishing proof that the action of the antitoxic serum is of the nature of a true chemical reaction, the following facts must be accepted as conclusive evidence that the result is due to the operation of laws which govern all other chemical reactions:

1. The neutralization or saturation of the toxin by the antitoxin occurs in the test tube as well as in the animal body.

2. It is more rapidly effected by mixing together strong solutions than weak ones.

3. It occurs more quickly under warmth and is proportionally retarded by cold.

4. A very marked elevation of temperature always accompanies the reaction *in vitro*, the degree of heat having been accurately measured by Arrhenius and Madsen, who found it to correspond to about half the elevation which follows the neutralization of a strong acid by an active alkali.

5. It has been proved experimentally that the toxin and antitoxin do not perish, or are not destroyed by the chemical combination; though the former is deprived of its injurious property for the time, it can afterwards be recovered from the solution.

6. The neutralization of the toxin has been demonstrated to proceed in obedience to the law of constant proportion; that is to say, a given amount of the chemical poison, or multiples of this amount, are always saturated by corresponding multiples of antitoxin—a fact which alone would establish the purely chemical basis of the reaction.

7. If the tetanus toxin be mixed with an emulsion of the brain of a healthy guinea-pig it becomes innocuous, chemical combination being thus brought about between it and the nerve protoplasm, probably in the exact manner in which this takes place in the living animal after injection of the poison.

These indisputable facts, if they cannot be accepted as proof that all other drug action is the result of a chemical combination between the drug and a compound radical with unsaturated affinities in the protoplasmic molecule of the selective cells, nevertheless must be accepted as going a long way in this direction. That proof is so conclusive in this instance of serum-therapy where the chemical structure is so very highly complex is not without significance. (I may incidentally mention that if the result of the action of strychnine be due to a chemical combination between the alkaloid and the cell protoplasm in the spinal cord, this hypothesis should be proven if previous trituration with nerve matter rendered the poison innocuous, as in the tetanus experiment. I regret to state that a long series of experiments, inaugurated by me some years ago, failed to establish this result, the failure being probably due to the alkaloid being prevented in gaining an access to the cellular protoplasm, owing to the cessation of some preliminary physical or chemical process in abeyance in the dead protoplasm.)

The purpose, however, with which I have set out in these remarks is not so much to heap up examples in support of a purely chemical theory of the action of drugs as to point to the influence of the hypothesis on the most recent trend of therapeutic progress. If we find that by following this conception as a working hypothesis pharmacologists have been able to achieve a notable triumph over disease, we may then safely accept its truth after the manner in which the chemical explorer accepts the molecular theory.

In this consideration a study of the evolutionary steps in the side-chain hypothesis affords a considerable degree of interest. It started in Ehrlich's mind on observing the effects of various staining agents on different parts of the animal cell. After studying the chemical structure of the dye molecule he was led by the laws of reasoning to apply his inferences to the explanation of the phenomena of immunization, and it is a most noteworthy fact that he at first denied the possibility of any similarity between the action of a chemical substance of known composition and of an antitoxin. He was, however, inexorably led by his research work to the conviction that the protoplasmic molecule possessed chemio-receptors which united with the haptophore or anchoring groups in the drug.

Dixon argues with a brilliant *naïveté* that since these hypothetical receptors are obviously distinct from food receptors it is difficult to regard them teleologically as pegs specially designed for the physician on which to hang his drugs. From a consideration of the results achieved it must be conceded that they are pegs strong enough to support the heavy superstructure of chemio-therapy, the coping stone of which at present is neosalvarsan.

Led first by the truth of the generalization arising from the research of Crum Brown and Fraser, Ehrlich proceeded on his path of exploration by applying at each step his side-chain hypothesis to the elucidation of the complex reactions occurring in the human body after the

injection of various dye stuffs and a host of arsenical compounds, with the result that he was enabled to discover an agent possessing the maximum parasite-destroying power with the minimum of organotropic action. But this was not all; the blending of the solution of two problems which confronted him is to be seen when we examine his final achievement. He had not only to solve the problem of killing the parasite without injuring the patient, but he had to cure the disease, which was liable to be aggravated seriously by the rapid disintegration of the slain spirochaetes. In his method we find chemio- and sero-therapy working side by side, the one aiding the other. A dose of salvarsan injected into the veins of a syphilitic mother effects the dissolution of the parasites, whose liberated toxin at once leads to the formation of antibodies in the parental blood, these on being conveyed to the infant in the mammary secretion destroy its myriad spirochaetes or render their propagation impossible, as in the diphtheritic disease, even when no trace of the salvarsan molecule can be detected in the mother's milk.

In establishing chemotherapy, Ehrlich's aim was to effect a complete sterilization of the body by a single full dose of the antiparasitic drug without injuring the tissues, a result which he designates the *therapia sterilisans magna*. It is a very remarkable fact that in both this result and in the chemical combination theory which led to its achievement, he was forestalled by Binz of Bonn in a most important research made in 1867, the year previous to Brown and Fraser's discovery.

Binz, when experimenting on the action of various drugs on the infusorial organisms met with in ordinary hay infusions, discovered that active paramoecia were readily destroyed by a 1 in 10,000 solution of quinine, though they withstood the action of enormously stronger solutions of strychnine and other poisons of vegetable origin.

Three momentous conclusions were drawn from this simple experiment: First, that the cause of malaria, which was then unknown or dimly guessed at as a nervous manifestation, would probably be found to be of protozoan nature, since malarial disease was so readily cured by quinine. Secondly, that by administering 15 grains of the hydrochloride to an average man a solution of twice the strength in the blood necessary to kill amoebae was formed, thus fulfilling the ideal of *therapia sterilisans magna* of Ehrlich. Thirdly, at a later period the working hypothesis of true chemotherapy was applied, by which it was inferred that the quinine entered into chemical combination with the protoplasmic molecule of the parasite, whereby it was robbed of its power of absorbing oxygen, and died of asphyxia.

Though Binz's work was mainly empirical and not conducted upon the purposive lines of Ehrlich's researches, nevertheless it affords us evidence that he was but dealing with another glimpse of the seamless garment of an eternal truth which will be found ultimately to clothe all drug action as well as every mysterious metabolic process in the living body.

From a consideration of the chemical basis of serum-therapy one is naturally led to test the value of this working hypothesis as affording an explanation of the advances made in vaccine-therapy by Wright. We shall pass lightly over these brilliant achievements, not because they are of less importance, but because the progress made in this direction does not very obviously appear from Wright's published writings to have been started entirely by the impulse of a chemical theory, as was the case in the more apparently purposive scheme of Ehrlich's researches.

The recent Witwatersrand Report of Sir Almroth on "The Treatment of Pneumonia" gives no uncertain note about his views on this subject and forces us to believe that vaccine treatment owes its origin to the conception of a true chemical combination occurring between the remedial vaccine and the bacterial protoplasm. Thus, he states that there is within the human body a laboratory which can, within certain limits, furnish bacteriotropic substances which will enter into destructive chemical combination with any and every variety of bacterial protoplasm without poisoning the tissues or becoming inert in the blood. All immuno-therapy and, in particular, all vaccine-therapy has been built up, he says, "upon these

facts and upon the fact that the chemical machinery which elaborates bacteriotropic substances is set in motion whenever a chemical attack is made upon the tissues by dissolved bacterial protoplasm." He objects to the term "chemiotherapy" being restricted in its application to specific treatment by drugs, since, in all cases, both in serum and vaccine treatment as well as in specific drug therapy, the attack upon the microbes is a *chemical* attack.

A host of workers has already been busy with the test tube and the chemical balance in this department of investigation, guided by the side-chain theory, so that the mysteries of vaccine action and its allied phenomena are being steadily cleared up. But the light let in upon the working of the process flows from the genius of Wright through the discovery of his own peculiar methods of demonstrating the possibility of measuring dosage and results by the opsonic index and other modifications of the phagocytic machinery.

The chemical reactions are much more complicated, and hence more difficult of demonstration than in the case of the simpler neutralization of a toxin by its antitoxin, because, as already stated, no true antibodies are produced during vaccine treatment. Nevertheless, the serum of an immunized animal will kill the corresponding bacteria when these are added to it *in vitro* though in a distinctly different manner from that by which the diphtheritic and tetanus antitoxin act.

Two substances are required for this destruction of the microbe; one of these, the so-called *immune body*, is produced during the injection treatment, the other, known as the *complement*, exists already in the normal serum, and is not elaborated in increased amount by the injections. The side-chain doctrine hypothesizes the immune body as possessing two receptors, one of which binds it to the bacterial endotoxin, whilst its second affinity satisfies itself by combining with the complement. The possession of this double affinity of the bacteriolysin is recognized in its name of amboceptor. It must be regarded as an intermediary body which (in the chemical language of Wells), on being added to the bacteria during the process of immunization, gives to them a chemical affinity for the complement existing already in the blood serum. It is therefore the complement and not the immune body which effects the destruction of the bacteria.

The sceptic may say that this explanation is pure fancy and that chemical laws have nothing to do with the result, but Hektoen has been able to isolate the complement and to prove that it is a definite chemical compound. He has rendered it inactive by causing it to combine with the ions of calcium, magnesium, and sulphuric acid, and Manwaring has succeeded in divorcing it from these ions by a simple chemical reaction. Other investigators have shown that it is a body which, though closely resembling an enzyme and very susceptible to heat, nevertheless combines with the amboceptor, in obedience to the law of definite or multiple proportions which prevails in every true chemical reaction.

The most inscrutable problem arising in serum therapy is the phenomenon of hypersensitiveness which appears on the reinjection of a serum, and causes death when all is apparently going well with the patient. Wolf-Eisner pointed out that the fatal result was due to the operation of a general biological law governing the action of a heterogeneous albumen, namely, that it causes the formation of reactive substances. It is a most noteworthy fact that, quite recently, this hitherto insoluble crux has been brought under the grasp of the chemical working hypothesis in a most unexpected way by Friedberger, who, by mixing quantitative proportions of antigens, antibodies, and complement obtained from healthy serum, was able to liberate the chemical compound which produces the tragic phenomenon of hypersensitiveness.

From these important discoveries which have established a true working theory for serum therapy, vaccination treatment, and hypersensitiveness, we derive faith that the long cherished hope of dealing effectually with all bacterial diseases will be soon realized, especially as it has been abundantly proven that the protoplasmic molecules of nearly all the pathogenic organisms possess receptors capable of combining chemically with various staining reagents.

Till quite recently it must be confessed that all the more

important advances in therapy left the greater problem of the treatment of the diseases caused by endotoxin microbes untouched. Neither did the triumph of salvarsan aid us directly, save by lifting therapeutics out of the old rut of empiricism by demonstrating what could be achieved by the application of rational methods based upon a sound chemical theory.

The fringe of the dark cloud which like a pall had overshadowed the therapeutics of the commoner bacterial affections has recently been lifted by the experimental researches of Morgenroth and his co-workers. Writing of these results, Wright states that "they are destined to stand out as a landmark in the history of pharmacotherapy, because they furnish the first demonstration of the possibility of preventing and curing a bacterial—as distinguished from a protozoal or spirochaetal—infection by the administration of a drug." The experiments were made by injecting mice with the pneumococcus, which always proved fatal when untreated. By injecting ethylhydrocupreinhydrochlorate before the inoculation 90 per cent. of the rodents were saved, and in 50 per cent. death was prevented when the salt was injected after infection. These results place the action of Morgenroth's agent in a totally different category from that of any known chemical antiseptic. When tested in the treatment of pneumococcal infections in man, though the new drug was found disappointing and was proved to produce optic disturbances, it affords us every reasonable hope that by proceeding on Ehrlich's rational lines a substitution product will be discovered capable of giving equal or better results than the startling effects on mice suffering from the same microbic infection.

A grave obstacle to the acceptance of a purely chemical hypothesis of drug action has hitherto existed in what we may term the bogey of catalysis and cell enzymes. Even this, however, has now been removed by the scientific explorer. The most recent researches into the nature of the highly complex chemical structure of the enzymes afford no clue to the plan of their constitution, which remains still a profound secret. All we know about them is derived from a study of their effects. They are to be found in every living cell, and the old view which maintained that all the metabolic phenomena of life were due to the vital activity of the cell is now shifted to the action of enzymes. These, even when intracellular, have in many instances been separated from the living protoplasm though in a state of only comparative purity.

Every known enzyme is undoubtedly in the first instance the product of a living cell, but the same may be said of quinine and strychnine, and the part played by the parent enzyme cell may be conceived by the demonstration of Robert, who procured chemically active trypsin from the body of a spider preserved for a century and a half in the Nuremberg Museum, as Sehrt discovered active glycolytic ferment in the muscles of a mummy. The researches of Croft Hill and Oswald have proved that the action of enzymes is simply a chemical one, thus the mystery of their behaviour, which a few years ago was regarded as the bulwark of the vitalist argument, has now been demonstrated to be nothing but a series of chemical reactions which are occurring in every cell in the body. The enzyme merely increases the speed of the reaction, which, like other chemical reactions, is reversible, the change occurring from either side of the equation till equilibrium becomes established. In this way, as clearly pointed out by Wells, enzymes not only hasten the splitting up of organic compounds, but they quicken synthesis, though both processes would go on without their presence, only at a much slower rate of progress. He sums up the results of our recent knowledge in the following words: "All metabolism may be considered as a continuous attempt at establishment of equilibrium by enzymes perpetuated by prevention of attainment of actual equilibrium through destruction of some of the participating substances by oxidation, or other chemical process, or by the removal from the cell, or entrance into it, of materials which overbalance one side of the equation."

If we could clearly prove that the action of enzymes is to be explained on a purely chemical basis, as has been done in the case of the toxin and antitoxin, it must be conceded that the way to a clearer chemical conception of drug action is opened up. I believe that this has been done, for the following reasons:

Though enzymes do not act quantitatively, they are, nevertheless, practically identical, pharmacologically, with true toxins—that is, with those chemical compounds which are the free secretion of bacilli. If a full dose of a sterile enzyme be introduced into the circulation, a profound toxæmia, terminating in death, occurs. When a smaller amount is injected and repeated in increasing quantities, immunization results from the formation of antibodies, which impart an anti-enzymatic property to the blood serum. This serum, when removed from the vessels of the immunized animal, is found to possess the power of neutralizing fatal doses of the enzyme injected into another animal, and appears to behave, in every particular, in the same manner as the antitoxin of diphtheria does with its toxin. Moreover, the anti-enzymatic action of the serum is rigidly specific, combining only with its own enzyme, as pointed out by Fidler.

It appears, therefore, impossible to escape the conclusion that the ferment contains a haptophore and toxophore group, which combine chemically with receptors in the molecule of the antiferment. This would probably apply also to the action of specific hormones, to which Dixon tentatively attributes the physiological activity of the tissues.

The importance of the acceptance of a chemical theory for the explanation of the action of enzymes affects the science of therapy much less than it does that of physiology and pathology. We realize this when we think of the modern biologist's view that the living cell must be regarded as a co-ordinated system of ferments, upon whose activities all the phenomena of life depend. Not only are they incessantly breaking down, but they are as continually building up or synthesizing new compounds and forming antibodies whose presence prevents the autodigestion of the different organs and tissues in the body.

To this broad conception of biological chemistry we might apply a modification of the old Greek's jest—The world is supported by Atlas, Atlas is supported by a tortoise, whilst *Chelonia graeca* itself is resting upon fair weather. E. J. Lewis has playfully suggested that the riddle of the world might be better figured by substituting the word "enzymes" for "fair weather," and I would venture to transform the burlesque into a scientific truth by suggesting that the enzymes are now resting finally upon the solid foundations of chemistry, whose laws govern—

"Air and ye elements, the eldest birth of Nature's womb, that in quaternion run, perpetual circle multiform; and mix and nourish all things."

Any survey of the potent factors in recent therapeutic advance would be very imperfect without a recognition of those purely physical forces whose fascinating influence is obviously manifesting itself on the mind of every explorer in each of the domains of natural science. I refer to those physical laws whose operations are seen in alterations of surface tension, osmosis, diffusion, dissociation, etc.

Our recently acquired knowledge of these forces sometimes proves a veritable *embarras de richesse* to the pharmacologist. Thus one of the latest arguments used for the support of the old physical view of drug action is derived from the study of the *modus operandi* of the hypnotics and narcotics by applying the theory of Hans Meyer and Overton. This postulates that the selective action of a narcotic depends upon its solubility in the brain lipoids, the more powerful members of the group being those least soluble in water and most soluble in fat. Traube's theory also runs on purely physical lines, since he attempts to explain the hypnotic action by assuming a difference of the surface tension, which alters the velocity and direction of the osmosis.

The applications of such theories may, with all respect to their supporters, be regarded as an illustration of the invisibility of the wood because of the presence of its trees. To the searcher after the truth of things such theories merely explain the entrance of the drug molecule to the cerebral cell protoplasm without affording us any help whatever regarding the way in which the narcotic effect is produced. To obtain this we must fall back on the chemical theory of Baglioni, which assumes that the temporary paralysis of the cerebral cell is due to the withdrawal of its life-giving oxygen, since the benzene-phenol compounds, in obedience to the law of relationship

between physiological activity and chemical constitution, exert their hypnotic action in inverse proportion to the amount of oxygen present in their lateral radicals. That such reduction explanation is almost certain to be true is proved experimentally by the fact that ether, chloroform, chloral, and alcohol reduce the oxidizing power of living cells. Moreover the physical theory of Overton and Meyer fails entirely to afford any explanation of the action of the most typical member of the group—alcohol.

The more closely we examine the physical and vitalistic conceptions of drug action the more certain does it appear that behind the operation of physical laws and vital activity, chemical reactions are continually taking place which are the real cause of the physical forces being themselves set in motion. Such a statement as this might at first sight appear to be bringing us perilously near to a futile discussion on the origin of life should we venture to define life itself simply as a form of chemical action as some have done. But it is quite another matter to recognize that the original fiat—"Let there be life"—effects its mysterious design through the operation of chemical laws aided by the physical forces which are to be seen in action everywhere around us.

As I draw these necessarily disjointed generalizations to a close, let me for a brief moment turn from the theories of drug action to a wider arena, where we may see in active operation all the forces which are probably also busily engaged in every pharmacological experiment. It will widen our horizon to realize what the application of a chemical hypothesis is doing for the science of pathology, upon which science only can we hope to build up a rational therapy. I will therefore ask you to glance at a subject which has engaged the attention of every pathological explorer since the advent of Virchow's conception of the cell being the structural unit of the living organism. I refer to the mechanism of inflammation. The most prominent and constant feature observable in the early stage of a local inflammatory process is the remarkable phenomenon of the invasion of the site of inflammation by hosts of leucocytes. Whence they come in such increased numbers into the circulating fluid we need not pause to consider; we are mainly concerned with the fact of their rapid swarming to the seat of injury. Why do they come? Can any explanation be given of their remarkable behaviour in penetrating the capillary walls and migrating far and near into the injured tissues? Whether we accept the earlier views of Metchnikoff and regard them as fighting cells or accept the later view of Baumgarten, which gives to them the position of grave diggers, we long for some light on the way in which they are seen to engulf foreign bodies such as bacteria or fragments of perished tissue.

Those who swallow the doctrine of vitalism have no difficulty in regarding each leucocyte as a sentient and discriminating gourmand who carefully selects and enjoys his food, who occasionally, disdaining the limits of his little reign, breaks bounds voluntarily, and may even seem in so doing to snatch a fearful joy. The scientist, however, explains easily the entire phenomenon in a perfectly rational manner by the application of the bio-chemical principle known as chemiotaxis.

It has been demonstrated that certain chemical substances powerfully attract the leucocytes, and these amoeboid organisms are seen to be drawn towards them when such compounds are brought anywhere near their zone. It appears to be absolutely certain that the immigration of the white cells into the site of an inflammatory action is determined by a chemical change in the protoplasm of the injured tissue or to the presence of a soluble chemical in its fluid constituents.

If any one doubts that the apparently volitional movements of a leucocyte cannot mostly be explained in this easy manner, he has only to resort to the simple experiment of manufacturing for himself an artificial amoeba and watching its extraordinary behaviour when various substances are brought into its presence. By placing a single drop of oil of cloves in a small dish partially filled with a mixture of alcohol and glycerine, the little bladder of oil floating on the surface will be found in structural and other peculiarities to conform to the type of an amoeba, and I have been able to form even vacuolated artificial amoebae by pouring chloroform into strong perchloride of iron solution.

Rhumblers' clove oil amoeba may be made to perform all the puzzling antics of a living leucocyte by gently injecting into the liquid in its immediate vicinity substances which alter the surface tension on one side of the sphere. In this manner it can be made to throw out pseudopodia like a living cell. A chloroform droplet in water can be repeatedly fed by various substances which it will take into its interior. If an insoluble solid, as a particle of quartz, coal, or glass, be coated over with a thin layer of shellac and presented to this artificial amoeba it is speedily swallowed, engulfed or surrounded, and after it has digested or dissolved its resinous envelope the droplet disgorges its indigestible prey. If the lac be offered in the form of a drawn out thin thread of sealing wax it will be seen to seize it by its middle and bend it, after which it throws out pseudopodia to the ends of the thread so as to pull the thread within itself by coiling it up in its interior till its solution, or we may say till its digestion, is completed.

The startling lifelike osmotic growths of Stéphane Leduc illustrate but another phase of the same phenomenon. These fantastic formations of dead sterilized chemical substances absorb food into their interior, break it up chemically, expel the waste products of the reaction, using only those necessary for their growth. They reject some chemical substances when offered to them and greedily absorb others; they grow up vigorously during their short-lived youth; remain stationary for a time, then die and suffer disintegration like living beings.

These phenomena of chemiotaxis and alterations in the surface tension so closely simulate life that many observers have ceased to hesitate to apply their action to the explanation of the behaviour of the leucocytes in the inflammatory area, though Jennings thinks that he sees a fundamental difference in the flow of the fluid contents. Each amoeboid leucocyte contains its own co-ordinated system of enzymes, the ceaseless activity of which is incessantly effecting changes of a chemical nature in the surrounding liquid medium by which the laws of surface tension and chemiotaxis are kept in constant action.

It is not only in the mechanism of the inflammatory process that chemiotaxis has been shown to play such a prominent part. From the biologist's point of view the crowning or supreme function of the living organism is seen in the phenomenon of reproduction. I need not remind you how Sir John Bland-Sutton, in the fascinating and original oration of last year, referred to the subject of gametic attraction, in which is witnessed the operation of some powerful and mysterious force by means of which the spermatozoon is drawn towards the passive yolk-laden ovum. Pfeffer experimentally demonstrated that malic acid strongly attracts the spermatozooids of various ferns when brought within their zone. Now, this substance has been found to be produced within the female sperm cell, and it can hardly be doubted that it is the agent which determines the actual contact of the male with the female elements of the cryptogam. It was to the discovery of this strange phenomenon that we owe the origin of the term "chemiotaxis"—a force which thus plays a leading part not only at the very inception of the life of the new individual, but all through his prolonged struggle against disease and final dissolution.

When we are thus enabled to realize the prominent part which chemical laws play in the phenomena of inflammation, and likewise also in the process of immunization, it cannot but aid us in accepting at least the high probability if not the actual proof of the force of such factors operating in all drug action. We then in renewed hope and strong faith can look forward to our arrival at the final goal of a rational therapy by travelling on the guiding lines which the genius of Ehrlich and of Wright has laid down for future research work.

THE late Dr. Alfred Chune Fletcher, Resident Medical Officer of Sutton's Hospital in the Charterhouse, left estate valued at £18,441.

THE Fourteenth International Antialcohol Congress will be held in Milan in September (22nd to 28th). The proceedings will be introduced by Professor Ettore Marchiafava, of Rome, with an address on the pathology of alcoholism. One day will be devoted to a discussion of the relations between the campaign against alcohol and the interests of viticulture.