SCIENCE

VOL. LX AUGUST 29, 1924 No. 1548

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SCIENCE: A Weekly Journal devoted to the Advancement of Science, edited by J. McKeen Cattell and published every Friday by

THE SCIENCE PRESS

Lancaster, Pa. Garrison, N. Y.

New York City: Grand Central Terminal.

Annual Subscription, $6.00. Single Copies, 15 Cts.

SCIENCE is the official organ of the American Association for the Advancement of Science. Information regarding membership in the association may be secured from the office of the permanent secretary, in the Smithsonian Institution Building, Washington, D. C.

Entered as second-class matter July 18, 1923, at the Post Office at Lancaster, Pa., under the Act of March 3, 1879.

PROGRESS AND PROSPECTS IN CHEMOTHERAPY[1]

IN the mind of every physiologist visiting Toronto to-day one recent advance in our science will certainly be uppermost. We rejoice with our colleagues here in a great achievement which has opened new vistas of knowledge to exploration, has brought relief to unmeasured misery, and has turned the eyes of a world, too often careless of such things, in proper gratitude and well-founded hope to this university and its medical school. Insulin, and its still marvelous and mysterious action, have held a prominent place in the interest of many of us, myself included, during the past year or two. In one of our meetings, however, we shall have the opportunity of considering the observations and opinions of many who are now working on its properties and their significance, and among them will be some who were associated with its discovery. I have thought it appropriate, therefore, to ask your attention to-day to some recent developments in a widely different field of investigation. The subject which I have chosen presents points of general physiological and biochemical interest, apart from its immediately practical importance for the treatment of disease. It has, further, in one way, a special appropriateness to this year's meeting of the British Association. For our knowledge of an important group of diseases, caused by the parasitic trypanosomes, which have provided the experimental material for a very large proportion of chemotherapeutic investigations, we are in the largest measure indebted to the pioneer work of the distinguished president of the association, Sir David Bruce.

THE THEORETICAL ORIGIN OF CHEMOTHERAPY

Chemotherapy may be defined as the specific treatment of infections by artificial remedies. The object of those who study it is to find new remedies which will cure or arrest diseases due to infections, not by alleviating the symptoms or invigorating the patient, but by directly and specifically suppressing the infection. Chemotherapy, in this wide sense, is not entirely of recent growth. When the natives of Peru discovered the value in fevers of the cinchona bark, which the Jesuits brought to Europe in the 17th century, they had found a specific remedy for malaria, which is still the best available. Similarly the natives of Brazil had found in ipecacuanha, which reached

[1] From the address of the president of the Section of Physiology of the British Association for the Advancement of Science, Toronto, August, 1924.

Europe shortly after cinchona, a remedy for amoebic dysentery better than any other which our modern systematic and scientific efforts have produced. Modern chemistry, indeed, has separated the alkaloids from these drugs, and has made it possible to identify among them the actively therapeutic constituents; protozoology has revealed the nature of the infections. We know now that cinchona owes its curative action chiefly to quinine and quinidine, and that they act as specific exterminators of the malaria parasites, and not simply as remedies for fevers in general; and we know that ipecacuanha owes its action to emetine and cepheline, and that these act as exterminators of the entamoeba causing tropical dysentery, and not simply as symptomatic remedies for dysenteries of any kind. But chemistry has produced no better remedy for malaria than quinine, or for amoebic dysentery than emetine; and the method by which either of these alkaloids cuts short the infection by a particular parasite, the nature of its specific action, remains a fascinating problem.

The modern development of chemotherapy, as a new department in therapeutic science, claiming the cooperation of parasitologists, microbiologists and synthetic chemists, did not take origin, however, simply from the study of these traditional remedies. It may be regarded rather as an outcome of the study of the natural antibodies. The investigation of these natural antagonists to infection produced a new therapeutic ideal. Not only had they shown themselves to have an intensely specific affinity for the infecting organism of the toxin which caused their production; they were also perfectly harmless to the patient, behaving, in relation to his organism, as normal constituents of his body fluids and tissues. Ehrlich aptly compared them to magic bullets, constrained by a charm to fly straight to their specific objective, and to turn aside from anything else in their path.

Of the artificial remedies, on the other hand, which man had empirically discovered, even of drugs like those just mentioned as being specific for certain infections, the best that could be hoped was that they would eliminate the parasite before they poisoned the patient. And thus, when the limitations of natural immunity were becoming clearer; when it was realized that to certain forms of infection, several of which had proved to be infections by protozoa, the body was unable to produce antibodies of sufficient potency to eliminate the infection and leave the patient immune; the question arose whether, with the new and growing powers afforded by synthetic chemistry, man could not so far rival nature's achievements as to produce in the laboratory substances specifically adapted to unite with and kill the protoplasm of these parasites, as the natural antibodies united with that of others, and to leave the tissues of the patient similarly unaffected. The ideal of this new and systematic chemotherapy, as the imaginative genius of Paul Ehrlich conceived it, was to be the production by synthesis of substances with a powerful specific affinity for and a consequent toxic action on the protoplasm of the parasites, and none for that of the host—of substances, to use Ehrlich's own terminology, which should be maximally parasitotropic and minimally organotropic.

I want to invite your attention to-day to the results which during the last twenty years have been produced under the stimulus of this bold conception; not, indeed, to attempt a survey or summary of all that has been done, but, in the light of a few of the suggestive facts which have emerged, to consider how far this hypothesis has justified itself, and whether it can be accepted as a safe guide to future progress, as it has undoubtedly provided the initiative and working basis for much of what has been accomplished hitherto. Before we deal with some of the actual results obtained, it may be well to consider a little more closely what Ehrlich's working hypothesis involved. The problem was to discover, by chemical synthesis, a compound which, in virtue of its chemical structure, should have a maximal affinity for the protoplasm of a microscopic parasite, such as a trypanosome, and a minimal affinity for that of the host's body cells. These affinities were pictured by Ehrlich, in the terms of his side-chain theory, as determined by certain side-chains of the complex protein molecule, or chemoreceptors, which endowed the protoplasm with specific combining properties. When it is remembered that knowledge of the chemistry of the protoplasm of a trypanosome is almost nil, and that what little we do know suggests that it is very similar to that of our own cells, it will be admitted that the enterprise was one calling for scientific courage and imagination in the highest degree. Complete failure would not have been surprising; the matter for surprise, and for admiration, is that so large a measure of practical success should, at the end of two decades, already claim record.

TRYPANOSOMES AND SPIROCHETES

The Action of Dyes and Analogous Compounds

The investigations leading, in the last few years, to a clear promise, at last, of the successful treatment of the diseases in man and animals due to infections with trypanosomes, had at least two different starting-points, the action of dyes and the action of arsenic. Ehrlich's early interest in the synthetic dyes and his observations of the curiously selective distribution which they often exhibited among the cells and tissues of the body naturally suggested the possibility of finding in this group a substance which would selectively fix itself to the parasite and poison its protoplasm without injuring that of the host. The tech-

nique developed by Laveran and Mesnil, by which a particular strain of trypanosomes could be passed through a series of mice or rats, and produce an infection of standardized type and virulence, enabled the effect of a large selection of dyes to be investigated, with the view of finding one which would favorably influence the infection. A starting-point having been obtained, the resources of synthetic dye production were available to produce an indefinitely long series of derivatives and modifications of the active compound, each to be tested in its turn. In this way Ehrlich and Shiga arrived at a substance which gave experimental promise of curative value, a benzidine dye to which the name "Trypan red" was given.

Two years later, Mesnil and Nicolle, proceeding further along the same path, described an even more favorably active blue toluidine dye, "Trypan blue." This is the only one of the dyes which has hitherto had a genuine practical success in the treatment of a protozoal infection, not indeed by a trypanosome, but by an intracorpuscular parasite of the genus Piroplasma, which infects dogs and cattle. This successful application of Trypan blue to an animal disease has a special interest for us to-day, in that it resulted from the joint labors of last year's president of this section, Professor Nuttall, with a Canadian collaborator, Dr. Hadwen.

We may turn aside at this point to inquire how far the results even of these earlier investigations corresponded with the theory which gave them their impetus. Did these dyes really act by selectively staining and killing the parasites, and leaving the host's cells untouched? The evidence was certainly not in favor of such a view. Ehrlich and Shiga themselves observed that Trypan red, even in relatively high concentrations, was practically innocuous to the trypanosomes outside the body. The trypanosomes, like other cells, were not stained by the dye until they died, and there was no clear evidence that they died sooner in the Trypan-red solution than in ordinary saline. Again, Trypan red cured an infection by the trypanosome of "Mal de Caderas" (*T. equinum*) in the mouse, but not the same infection transferred to the guinea-pig, rat or dog; nor did it cure an infection with the trypanosome of Nagana (*T. brucei*) in mice. Now, to explain such a difference by stating that the affinity of Trypan red for *Trypanosoma equinum* was much higher than its affinity for the tissues of the mouse, but not than its affinity for those of the rat, would be merely to restate, in terms of the theory, the observed fact that the mouse was cured while the rat was not; and the lack of direct affinity for the dye shown by trypanosomes outside the body made such an interpretation in any case unsatisfactory. One point, however, appeared very significant, and it is met repeatedly in studying the action of effectively chemotherapeutic substances, namely, that the trypanosomes treated with the dye *in vitro*, though neither obviously stained nor visibly harmed, had lost their power of infection, and died out promptly if introduced into the body of a mouse. Under such conditions only minimal traces of the dye are introduced into the animal, and we are left with a series of alternative possibilities. It is possible that sufficient dye has been taken up by the trypanosomes to kill them eventually, the period of survival *in vitro* being inadequate to display its action; or that Trypan red is converted by the influence of the body fluids and tissues into something which is effectively lethal for the parasite; or, again, that the effect of the drug is not directly to kill the trypanosomes, but, leaving their individual vitality and motility unimpaired, so to modify them that they have lost the power of rapidly reproducing themselves and invading the fluids and tissues of the mouse's body—in other words, have lost that complex of adjustments to the various factors of the host's natural resistance which we crudely summarize as "virulence." Such possibilities involve either storage or modification of the dye by the host's tissues or their essential cooperation in its curative effect.

One other active dye must be mentioned as providing the link with a recent, most important advance. Mesnil and Nicolle in 1906 made some promising experiments with a dye, Afridol violet, which differed from any previously tested in that its central nucleus was diamino-diphenyl-urea. From this time onwards there was no further public indication of progress along these lines until 1920, when Händel and Joetten published the results obtained with a remarkable substance which, as the result of some fifteen years of continuous work by their scientific staff, had been introduced by the great dye and chemical firm of Bayer. This substance, which is not a dye, but the colorless, water-soluble salt of a complex sulphonic acid, has hitherto been known as Bayer "205," and, for reasons which need not concern us, the firm decided not to publish its formula. To students of their patent specifications, however, it seemed pretty certain that it would prove to be one of a long series of compounds, formed of chains of aminobenzoyl radicles, united by amide linkages, with a central urea linkage, like the dye last mentioned, and terminal naphthylamine sulphonic acid groupings. A number of these substances, having no diazo-linkages, were not dyes, but there was no indication as to which constitution, out of an immense number possible, would prove to be that of the remarkable substance numbered "205." There is a reasonable probability that its identity has now been settled by the recent work of Fourneau and his coworkers in the Pasteur Insti-

tute, who made and investigated an extensive series of compounds of this general type, and found one, which they numbered "309," which conspicuously excelled all others, even those closely related to it, in the favorable ratio which it displayed between a just toxic dose and that which caused a trypanosome infection in mice to disappear. As in the case of "205," the ratio, the "chemotherapeutic index" of Ehrlich, was found by Fourneau in some experiments with his compounds to be well over 100. At least it may be said that, if M. Fourneau has not identified Bayer "205," he has discovered another compound having very similar and probably as valuable properties.

The most remarkable property of "205" is the long persistence of its effect. A dose injected into a mouse, a rabbit or a rat will not only free the animal, if already infected, from trypanosomes in a few days, but will also render it resistant to such infection for a period of weeks or even months. During that period its serum, or extracts from certain of its organs, exhibit a curative action if injected into another animal infected with trypanosomes.

Though there seems no reason to doubt that this substance has cured a number of cases of African sleeping-sickness in man, even some in which the disease was well advanced and in which all previously known remedies had failed, the mode of its action still presents a number of attractive obscurities. Like many other remedies which are experimentally efficient when injected into the infected animal, it has little or no obvious action when directly applied to trypanosomes *in vitro*. The paradox is, perhaps, less than usually significant in this case, since the action in the animal is delayed, a period of a few days elapsing before the trypanosomes begin to disappear from the blood. We might suppose that the action is too slow to be recognized during the period of survival of the parasites outside the body, or that it affects not the individual vitality of the trypanosomes, but their power of reproducing themselves. The latter idea is supported, as in other cases, by the fact that trypanosomes treated with the drug *in vitro*, or taken from an injected animal before the curative effect has become manifest, fail to infect another animal. It is contradicted, however, by the observation that the trypanosomes, just before the curative action begins, show not a depression, but a stimulation of reproductive activity, division forms becoming abnormally common. Is it that during or immediately after division the parasites become specially liable to the action of the drug? It may be so; but one thing seems perfectly clear, namely, that the action is a very complex one, involving the cooperation, in some way, of the host. For here again it is found that the curative action, on infections by the same strain of trypanosomes, varies enormously with the species infected, a mouse being cured with ease, an ox or a horse with difficulty or not at all. A curious fact is that the rapidly progressive and fatal infections produced in mice by certain pathogenic trypanosomes are easily and certainly cured, while the apparently harmless natural infection, seen in many wild rats, by *T. lewisi* is not affected at all. Then there are some curious records of treatment in man, in which the symptoms of sleeping-sickness have disappeared, but the trypanosomes are still found in the cerebro-spinal fluid, suggesting that, though the parasites have not been killed, they have lost their virulence and their power of invading the brain substance.

The features of the action of this remedy, however, which have most interest for the physiologist and the biochemist are those related to the long persistence of its effect. "205" has a large molecule, but it is extremely soluble in water and diffusible through collodion membranes. How, in such circumstances, can we explain the persistence of its sterilizing and prophylactic action for months after an injection? At first sight one is tempted to regard it as incredible that a substance with these properties should persist in the body for such a period, and to suggest that the action must be due to its stimulation of the body to form its own protective substances. This possibility, however, seems to be excluded by the fact that the serum of the protected animal does not lose its curative properties if heated. On the other hand, there have recently appeared, some of them only in preliminary abstract, a series of highly suggestive observations, indicating that "205" has properties of entering into a combination of some kind with the serum proteins. After standing for an hour or two in serum, "205" no longer passes into an ultra-filtrate through collodion, and if the proteins are coagulated by heat is not to be found in the filtrate. The proteins of the blood, moreover, are stated to lose many of their characteristic properties by entering into this combination, the blood losing its normal power of clotting and the serum proteins not being precipitated by mercury salts or tannin.

It would be both useless and presumptuous for a mere onlooker to speculate in detail on the significance, for the curative action of "205," of properties which are only now beginning to be investigated. One conclusion, however, I think we are entitled to draw. It is sufficiently evident that here is no question of a substance curing simply on account of its affinity for parasites and lack of affinity for the host's tissues. What direct action on the parasite "205" itself may possess has still to be demonstrated; we may feel reasonably certain, on the other hand, that its affinities for the constituents of the host's blood and tissues play an important part in its remarkable and peculiar curative properties.

Derivatives of Arsenic

In the case of the other series of investigations which I mentioned, that dealing with the organic derivatives of arsenic, we find again many difficulties, in the way of the simple theory, of a cure due to distribution by chemical affinities. None of the compounds of this series, which have reached practical trial and success in the treatment of spirochetal or trypanosomal infections, atoxyl, salvarsan or tryparsamide, has a directly lethal action on the parasites in dilutions at all comparable to those which can be safely and effectively produced in the body of the host. The paradox of this direct inertness of atoxyl, the starting-point of the series, seemed to be explained when Ehrlich showed that its reduction to the corresponding arsenoxide produced a substance with an intense directly lethal action on trypanosomes. Similarly, the partial oxidation of salvarsan, to the corresponding arsenoxide, produced a substance having the intensely lethal action on spirochetes or trypanosomes *in vitro,* which salvarsan itself conspicuously and paradoxically lacked. In these cases, we may make the supposition, which Voegtlin and his coworkers, especially, have recently supported by detailed evidence, that the reduction or oxidation effected by contact with the tissues is the essential preliminary to the curative action; a supposition which, it will be noted, again introduces the host as an essential participant in the cure. The fact that the administration of these relatively inactive predecessors is therapeutically more effective than the injection of the directly active oxides derived from them would then be explained on the assumption that the slow liberation of these latter in the body, at a rate which never produces a high concentration, provides the optimum condition for their persistent action on the parasites without danger to the host. This slow and persistent liberation of the directly active substance would be favored by the physical properties of salvarsan, which at the reaction of the body is practically insoluble, and must be rapidly deposited after injection.

In their recent work on the action of Tryparsamide, the compound prepared by Jacobs and Heidelberger at the Rockefeller Institute which has shared with Bayer "205" the credit of making the eventual conquest of African sleeping-sickness a hopeful possibility, Brown and Pearce find it necessary to introduce yet other considerations to explain its effects. Tested by Ehrlich's therapeutic index—the ratio between the lowest curative and the highest non-toxic dose—it gives a relatively unfavorable figure. Brown and Pearce practically abandon the attempt to account for its action on the supposition that it directly kills the parasites and attribute its value largely to its power of penetrating easily into the tissues and reinforcing there the processes of natural resistance.

Action of Bismuth

Another conception of the mode of action of these arsenical remedies, also involving a direct participation in the host's tissues, was put forward by Levaditi. He found that from atoxyl a directly parasiticidal preparation could be obtained by incubating it with an emulsion of fresh liver substance. As the first step, therefore, in the curative action of atoxyl, he postulated a combination of its reduction product with some constituent of the liver or other tissue, giving rise to the essential curative complex, which he named "trypanotoxyl." Levaditi's observations were explained by Ehrlich and Roehl as due simply to the reducing action of the liver substance on atoxyl; but it would be difficult to apply this explanation to the quite recently published observations by Levaditi and his colleagues on the mode of action of bismuth in curing spirochetal infections. A sodium potassium bismuthyl tartrate—a bismuth analogue of tartar emetic—had been found to have valuable curative properties in syphilis and other spirochetal infections. Later, various other bismuth salts, bismuth suboxide and even finely divided metallic bismuth were found to produce similar effects. According to Levaditi and Nicolau, these preparations have, by themselves, a relatively weak action, or none at all, on the spirochetes outside the body. If they are mixed, however, with a cell-free extract of liver, which is itself harmless to spirochetes, the mixture, after incubation, acquires a potent spirocheticidal action. The possibility of a mere reducing action of the liver extract seems here to be excluded, since bismuthous oxide or metallic bismuth itself yields a spirocheticidal mixture, containing Levaditi's hypothetical "bismoxyl," when incubated with the liver extract. If these observations are confirmed, there will be a strong indication that some cell-constituent enters into the composition of or is essential to the formation of the directly active substance from any of the derivatives of arsenic, antimony or bismuth, as a preliminary to its action on an infection due to a trypanosome or a spirochete. Again we have evidence of an organotropic property of the remedy, as an essential condition of its activity.

Resistant Strains of Trypanosomes

In the phenomena of the acquisition of resistance, by a strain of infecting trypanosomes to a particular curative drug, discovered and largely worked out in Ehrlich's laboratory, we meet again with facts which can only with the greatest difficulty be reconciled with the assumption that the drug directly attacks the parasites. It was found, for example, that if a mouse infected with trypanosomes received an incompletely effective series of doses of atoxyl, the trypanosomes appearing in the blood at each relapse were more

and more resistant to the drug, unitl they could not be caused to disappear by any dose of atoxyl which the mouse would tolerate. The strain, having once acquired this resistance, would retain it, on passage through an indefinitely long series of mice, without further treatment. Mesnil and Brimont, however, made the remarkable observation that, if the strain of trypanosomes was transferred to a rat, it immediately became in that animal susceptible again to treatment with atoxyl, remained so as long as it was kept in rats, to reacquire its old resistance to atoxyl as soon as it was retransferred to mice. Such a fact seems to be not at all explicable on the theory that the directly active agent, to which the trypanosome becomes resistant, is a mere reduction product of atoxyl; it is much more easily reconciled with a mechanism such as that described by Levaditi, in which a constituent of the host's tissues enters into the formation of the trypanocidal substance. We can imagine the trypanosome becoming immune to Levaditi's mouse-trypanotoxyl, and remaining susceptible to the corresponding rat-product.

The whole question of this acquired resistance of the parasites to the action of curative drugs bristles with points of difficulty and interest. Ehrlich attributed the sensitiveness of the parasite, for a particular curative agent, to the possession by its protoplasmic molecule of a special form of side chain, or "chemoreceptor," which determined its affinity for that agent. When the trypanosome became resistant, it was simple to suppose that it did so by losing the appropriate chemoreceptors; an atoxyl-resistant trypanosome, for example, had lost its atoxyl receptors. Apart from the objections already mentioned, this conception met a new difficulty, when in Ehrlich's laboratory it was found that the resistance was by no means as rigidly specific as it had first appeared to be. Not only imperfect treatment with atoxyl, but treatment with a particular group of dyes, having no kind of chemical relation to it, was found to produce a race of trypanosomes resistant to atoxyl and to other arsenical derivatives. To suggest that the chemoreceptors for arsenic and for these dyes are identical is merely to restate the fact of this reciprocal action in terms having no definite meaning. Obviously no more precise conception as to its significance can be formed until we know something more of the conditions on which resistance and susceptibility depend. A recent suggestion by Voegtlin has interest in making, at least, an attempt at interpretation in more definite biochemical terms. Voegtlin and his coworkers point out that arsenious oxide and its derivatives readily combine with substances containing a sulphydrile grouping and find that the toxic action of the organic arsenoxides on trypanosome and mammal alike is depressed by the simultaneous injection of excess of various sulphydrile compounds.

Suggested Reaction of an Arsenoxide with a Sulphydrile Compound

The work of Hopkins, showing the importance of one such sulphydrile compound, reduced glutathione, in the hydrolytic oxidation-reduction processes of the cell, suggests to Voegtlin that a combination with such groups and consequent suppression of this vital function may explain the toxic and curative actions of the arsenical derivatives and that a formation by the trypanosome of the sulphydrile compound, in excess of its vital need, may be the basis of acquired resistance. If certain dyes similarly affect this cellular oxidation system, the production under their influence of strains of trypanosomes resistant to arsenic would also be explained. So stated the suggestion leaves many aspects of the problem still unconsidered; but it may at least be allowed the merit of an attempt to interpret the action of these drugs in terms of known biochemical facts.

Conclusion

We have considered but a few examples of the directions in which chemotherapeutic investigation has proved practically fruitful, including some in which it shows, at the moment, the most hopeful signs of progress. If one considers any one group of investigations by itself, one may easily feel, at the same time, elated by the practical success obtained, in the cure of some infection which, but a few years ago, seemed beyond the reach of treatment, and depressed by the disharmony between the results of experiment and the theoretical conceptions, hitherto available, of the nature of the chemotherapeutic process. Some of the most notable practical triumphs in this field have resulted not from experimental investigations based on theory but from an almost empirical trial on human patients suffering from one type of infection of a remedy which had experimentally shown promising results in infections of a different and sometimes of a widely different type. The partial success of tartar emetic in trypanosome infections might have justified a hope that it would have some effect in kala-azar but hardly a prediction of its really remarkable efficacy in that previously intractable form of infection. Still less would it have justified expectation of the brilliant success of this same drug in infections by the Schistosoma or Bilharzia-worm, which but recently seemed almost beyond the hope of any kind of treatment. With such instances in mind, one might, but a year or two ago, have been tempted to suggest that the attempts at theoretical investigation of the intimate mechanism of the chemotherapeutic process had contributed little to the practical achievements, and that a reasonably intelligent empiricism was still the safest guide. I do not think that the suggestion would even then have been defensible, and it would assuredly have been stultified by the results

of the past few years. Patient, systematic exploration, by routes of which the initial sections were already mapped in the early days of chemotherapy, has in these recent years again led to results of major importance, both for practical therapeutics and for the theoretical basis of future advance. That the original theoretical framework begins to show itself inadequate for the expanding fabric is good reason for its reconstruction; but we may well beware of hasty and wholesale rejection, remembering that it served the early builders well. I think that it is especially encouraging to note that, though, in the action of almost every remedy which has proved its value in the specific cure of infection, there are features which can not be interpreted by a strict application of Ehrlich's distribution hypothesis, the discrepancies begin to show a new congruity among themselves. Repeatedly we find phenomena which point to the need of modifying the theoretical structure in the same direction. The conception of a remedy not killing the parasites immediately, but modifying their virulence, or lowering their resistance to the body's natural defences; of a remedy not acting as such, but in virtue of the formation from it in the body of some directly toxic product, either by a modification of its structure or by its union with some tissue constituent; of an affinity of the remedy for certain cells of the host's body, leading to the formation of a depot from which, in long persistent, never dangerous concentration, the curative substance is slowly released; all these conceptions present themselves, again and again, as necessary for our present rationalization of the effects observed. It can hardly be doubted that they will potently influence the methods by which, in the immediate future, new and still better specific remedies are sought. But though our practical aim, in relation to the affinities of a remedy for the parasite and for the host's tissues, may be radically changed, the meaning of these specific affinities, so delicately adjusted to a precise molecular pattern, remains dark. Ehrlich's chemoreceptors may no longer satisfy us, but we have nothing equally definite to replace them. I have endeavored to indicate what seem to me hopeful signs of new contacts between biochemistry and chemotherapy. There is promise, in another direction, that at least some aspects of the problem of immune specificity are being brought within the scope of strictly chemical investigation, as in the recent work of Avery and Heidelberger, on the constituent of a pneumococcus which combines with the specific precipitin. As in Ehrlich's pioneer work in chemotherapy, it can hardly be doubted that an increased understanding of the meaning of immune specificity, which but a short while ago might have seemed hopelessly beyond the range of attack by chemical weapons, will still influence ideas and help to shape the course of further investigations on the chemotherapeutic process. As the biological complexity of the problem is realized, it becomes increasingly a matter for wonder and admiration that so much of practical value has already been achieved—the treatment of the spirochetal infections, syphilis, yaws and relapsing fever, revolutionized; Leishmania infections, kala-azar and Baghdad boil and Bilharzia infections which crippled the health of whole populations in countries such as Egypt, now made definitely curable; trypanosome infections, such as the deadly African sleeping-sickness, after years of alternating promise and disappointments, brought now at last within the range of effective treatment. And if such results have already been attained, in a period during which practice has often and inevitably outrun theory, we may well be hopeful for a future in which fuller understanding should make for more orderly progress.

H. H. DALE

DEVONIAN PALEONTOLOGY OF BOLIVIA

No geological system in South America has been so well explored as has the Devonian. The bead-roll of eminent contributors to the elucidation of South American Devonian paleontology commences with the name of d'Orbigny in 1842 and includes longer or shorter contributions by Salter (1861), Rathbun (1874, 1878), Hartt (1875), A. Ulrich (1893), von Ammon (1893), Katzer (1896–1898), Kayser (1897, 1900), Haug (1905), Thomas (1905), Newton (1906), and Knod (1908). John M. Clarke, whose labors in this field cover nearly a quarter of a century (1890–1913), and culminated in his magnificent monograph published in 1913, in which the whole field was covered in his characteristic masterly way, has contributed more than any one else to this subject.

The eastern South American Devonian has, on the whole, received more attention and more thorough treatment than that of the Andean region, although Devonian beds outcrop for hundreds of miles along the medial extent of the Andean system. The Devonian is well represented and fairly fossiliferous in Bolivia, in which general region d'Orbigny first collected Devonian fossils in South America, but these Devonian faunas have not heretofore received the exhaustive treatment that has been devoted to those of Brazil.

Last year there appeared in the Annales de Paléontologie a monograph of the Devonian of Bolivia by Roman Kozlowski,[1] who spent six years in Bolivia, first as a professor and subsequently as director of the School of Mines at Oruro. In this work there are described 138 different forms, making the Bolivian

[1] Kozlowski, R., "Faune Dévonienne de bolivie." Ann. Paléont., tome xii, 112 pp., 10 pls., 1923.