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EHRLICH'S CHEMOTHERAPY—A NEW SCIENCE[1]

HARDLY at any time in the history of modern medicine has there existed a more intense excitement and a more absorbing interest among the medical fraternity than at present. One of the greatest scourges of humanity—perhaps the most insidious and cruel of all, since it so often places its victims beyond the pale of human sympathy, to be loathed rather than pitied—is on the point of being eradicated. So abhorrent is the disease in the public mind that the press of the United States, which chronicled at great length the daily events in the life of Evelyn and Harry Thaw, feels constrained not to offend its readers by mentioning its name "syphilis," but hypocritically refers to it as a "blood disease."

The man to whom humanity is indebted for this achievement is Professor Ehrlich, of Frankfort-on-the-Main. This scientist is no stranger to chemists. As far back as thirty years ago Ehrlich employed organic substances, mainly coal tar colors, in his physiological studies. He discovered that methylenblue and its congeners were the only colors which stained the live nerve tissue, and in order to determine whether this remarkable property was due to the peculiar constitution of methylenblue or to the presence of the sulfur in it, he desired to experiment with an analogous substance in which the sulfur, however, was replaced by oxygen. He applied to Dr. Caro, who, alas for our science,

[1] Read before the New England Section of Society of Chemical Industry, Boston, October 7, 1910.

died last October, requesting him to assist in this work by furnishing the material necessary for the experiments. As the desired substance was then unknown, it was proposed to synthetize it by allowing nitrosodimethylanilin to react on metaoxydimethylanilin. This latter body being likewise unknown had to be prepared. Naturally the chemical thus originated was employed not only for the purpose suggested by Ehrlich, but also for all reactions for which analogous products had been previously used. One of the first experiments made was to try it in place of resorcin, to which it is closely related. The principal use of resorcin in the color industry was the manufacture of fluorescein by fusing it with phthalic acid anhydride. From fluorescein was made eosin, a particularly fine coloring matter. The Ehrlich product, however, gave in the same reaction a color even superior to eosin, namely, rhodamine, and in another reaction it furnished Nileblue.

Although originally a physician, Ehrlich, through steady pursuit of our science, developed into a most proficient and ingenious chemist, and by combining physiological with synthetic chemistry he created on their borderland the new science of chemotherapy.

To demonstrate to you the nature of chemotherapy, it is perhaps best to show what has hitherto been accomplished by Ehrlich and his school.

In the development of bacteriology, the science upon which are based the most important advances of modern medicine, the coal tar colors have played an indispensable part. These dyestuffs made possible the discovery of the dreaded microbes and their detection in disease. It was found that different bacteria manifested a selective affinity for different colors, some absorbing one and some the other, and this in itself now enables the scientist to distinguish between organisms belonging to the same group.

We know now that many, if not most, diseases are of parasitic origin, and that man and other animals are constantly at the mercy of these invisible enemies. Though attention has been devoted chiefly to the bacteria which belong to the lowest forms of vegetable life, modern research has brought to light the fact that certain diseases are due to protozoa or animalcules, which, on the other hand, constitute the lowest stage of animal existence. Among these disease-producing protozoa the most important that have thus far been discovered are the plasmodium, which causes malaria, the trypanosoma, a parasite which produces the African sleeping sickness, the ameba of dysentery, and the spirochete, the causative agent of syphilis.

It is a curious circumstance that although protozoa were discovered in the blood of various animals as far back as sixty years ago, that is even before the birth of bacteriology, it is only within the last ten years that their important rôle in the causation of disease has been appreciated. A number of causes have contributed to this, especially the fact that most of the maladies due to protozoal parasites occur in tropical countries, while bacterial diseases are constantly in our midst. The discovery of the malarial protozoa, the plasmodium, by Laveran, however, gave an impetus to this line of research, and this circumstance in connection with the special study that is being devoted to tropical diseases has already contributed materially to our knowledge of the origin of many hitherto obscure maladies.

More important than the discovery of the cause of a disease, however, is its prevention and cure. Fortunately, in the case of malaria empirical observation had

supplied a specific remedy, quinin, long before the discovery of the plasmodium. On the other hand, the study of the life history of this organism and the demonstration of its transmission through the bite of the mosquito, have rendered it possible to devise means for malarial prophylaxis. In the case of syphilis clinical experience during many centuries has demonstrated the value of mercury in controlling the manifestations of this disease, but although vaunted as a specific, this remedy can not be regarded a true curative agent, since it has failed to prevent recurrences from taking place, sometimes even after long periods.

One of the most malignant of this group of protozoal parasites is the trypanosoma, the cause of the dreaded sleeping sickness and of various diseases in horses and cattle, whose ravages, especially in the African colonies of England and Germany, make it one of the worst pests with which mankind is afflicted.

A brief description of these parasites will, perhaps, prove instructive. In the first place it must be noted that the trypanosoma has been found in the blood of many animals, both cold- and warm-blooded, and that some varieties of this parasite appear to be perfectly harmless. Those which are of particular interest, because of their virulence, are as follows: (1) *Trypanosoma evansi,* discovered by Evans more than twenty-five years ago, which is the cause of surra, a destructive disease of horses, camels, cattle and dogs prevailing in India as well as in other parts of Asia, and in the Philippines and Africa. (2) *Trypanosoma brucei,* discovered in 1894 by Bruce, which causes the very fatal nagana or tsetse fly disease of Africa in various domestic animals (horses, mules, dogs, cats, etc.), but like the preceding does not attack man. (3) *Trypanosoma equiperdum,* the cause of dourine, a disease affecting horses, but, unlike the above, found outside of tropical countries, particularly on the shores of the Mediterranean. (4) *Trypanosoma equinum,* the cause of mal de caderas, occurring almost entirely among horses in South America. (5) *Trypanosoma Gambiense,* the most important of this group, first shown to be the cause of human trypanosomiasis by Castellani in 1902. (6) Parasite of mbori, a disease of camels in the Sudan, especially in Timbuctoo.

Trypanosomes, while differing more or less in their special characteristics, have in common a worm-like body and are flagellated, that is, provided with a membranous sheath (undulating membrane) terminating in a slender whip-like process designed for locomotion. They are much larger than bacteria and can be seen with a comparatively low power of the microscope swiftly darting between the blood cells, brushing them aside, but not penetrating them like the parasite of malaria, the plasmodium. One of the most remarkable features in their life history is their manner of transmission. While infection with bacteria takes place directly, as through the air, food, water, or through a wound, the trypanosoma, like the parasite of malaria, requires an intermediary or complementary host, usually some blood-sucking insect, as the Indian horse fly or the tsetse fly of Africa. In the act of sucking an infected person or animal the insect draws up the parasite with the blood and carries it about in his proboscis, and later again injects it in biting another individual. While in the case of the plasmodium the parasite undergoes certain changes in the body of the insect, this has not been shown to occur with trypanosome, so that it is commonly believed that the

insect acts chiefly as a carrier of the parasite.

The trypanosome which is of particular interest on account of being the cause of sleeping sickness is the *Trypanosoma Gambiense*. It is disseminated by a species of tsetse fly known as *Glossina palpalis*, which somewhat resembles our common house fly. According to Koch, the *Glossina* subsists largely on the blood of crocodiles, and he recommended that these should be exterminated to reduce the number of insects. It has been shown by others, however, that the tsetse fly disease prevails in regions where there are no crocodiles, and, *vice versa*, that it is not met with in regions where these reptiles are abundant. Probably in the course of time some practical scheme will be devised for exterminating these insects similar to those in vogüe in regions infected by the mosquitoes which transmit malaria and yellow fever. The task will be more difficult because the young of the tsetse fly soon reach maturity, as they are born in the larval state instead of being deposited as eggs.

One of the great difficulties in the treatment of sleeping sickness has been that in its early stages the symptoms are so mild that the patients, chiefly ignorant natives, do not resort to medical aid. When seen by the physician, therefore, the disease is generally far advanced, the patient being emaciated, dull, apathetic, dragging along his limbs, but sleeping most of the time, a sleep which finally becomes a coma and terminates in the death of the unfortunate victim.

In the colonization of Africa one of the most important problems is the extermination of this dreaded disease, which is making constant inroads upon the native population, and which in some districts has carried off more than one half of the inhabitants. This increasing prevalence of the disease led the German government to send Professor Koch on a special expedition for its study. Excellent work in this direction has also been done by English scientists, especially the Liverpool School of Tropical Medicine, as well as by the French and Portuguese.

Unfortunately, the treatment of sleeping sickness and of the various trypanosoma diseases has been exceedingly unsatisfactory, but from the work accomplished by various investigators, especially Ehrlich, Laveran, Mesnil and Nicolle, there is sufficient ground for believing that in the coal-tar or the arsenical preparations will be found specific remedies or at least valuable auxiliaries. At any rate, the line of research which Ehrlich has been pursuing in this field demonstrates the superiority of the modern methods of treatment, which are based upon purely scientific deductions and not, as was formerly the case, solely upon empirical observations.

This new system of treatment is founded upon the study of the selective affinity which the various medicaments have for the tissues of the body and for the parasitic organism that may infest it. In the case of most drugs, however, it is difficult and even impossible to understand their selective action, since the changes they produce are for the most part imperceptible. For this reason Ehrlich at an early period of his studies was led to experiment with the anilin colors, since their effect upon those cellular structures for which they have an affinity could be easily determined by their staining property.

In this connection it may be mentioned that as long ago as 1890 Ehrlich, in collaboration with Leppmann, published some observations on the pain-relieving qualities of methylenblue, the correctness of which has since been abundantly confirmed

in practical medicine. In this country A. Jacobi has particularly called attention to this quality of the color and to its value in the treatment of inoperable cases of cancer. Later Ehrlich, in conjunction with Guttmann, experimented with methylenblue in malaria, and found it a true specific for the parasite of the quartan type of the disease, while it acted less promptly or failed in other varieties. In view of the difficulty, however, of experimenting with malarial organisms he found the trypanosoma much better adapted for his studies, since it can be inoculated in small animals, such as mice and rats. Since 1904, with the assistance of K. Shiga, he has tested many hundreds of various colors in order to determine their influence upon trypanosoma infection, and finally found among the benzidin group a color which, when administered to mice inoculated with the trypanosoma of mal de caderas, retarded the progress of the malady for several days. This result, though not decisive, was sufficiently promising to lead him to experiment with other synthetic products of the benzidin group. He finally discovered trypanred, which was found to exert an actual curative effect upon the above-mentioned trypanosoma. When trypanred was injected into mice twenty-four hours after they had been infected with the trypanosoma of mal de caderas, which ordinarily produced death in four to five days, it was noted that on the following day the parasites had disappeared completely from the blood, and the majority of the animals remained permanently cured. Sometimes, however, the parasites reappeared after a number of weeks, and then speedily caused the death of the animal.

These results were confirmed by Laveran and Halberstaedter with other parasites. The former inoculated mice with the parasite of mbori, the latter with the parasite of dourine.

Ehrlich's experiment therefore was the first which clearly showed that it was possible by means of an anilin color to free the body entirely of virulent parasitic organisms. Curiously enough, however, the trypanred which acted so efficiently in this respect in mice inoculated with trypanosoma of mal de caderas, had a much less favorable effect in other species of animals, even the rat, and against other varieties of trypanosoma, as, for instance, that of tsetse disease. On the other hand, Laveran and Franke showed that by combining arsenous acid with trypanred a curative effect could be obtained in conditions unaffected by the latter alone.

In order to improve trypanred, Ehrlich, together with Weinberg, tested a large number of substitution products of this substance, and found among them an amidotrypanred, which acted more efficiently than trypanred itself upon the virulent nagana parasite.

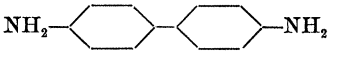
Mesnil and Nicolle, of the Pasteur Institute of Paris, continued Ehrlich's experiments with a large number of synthetic colors. Their first experiments were undertaken with a number of benzidin colors, the parasite selected for the test being the trypanosoma of nagana, the tsetse fly disease. This parasite was chosen because it is more refractory to trypanred than some of the others. These experiments, which were made upon mice, showed that certain blue or violet colors derived from 1.8 amidonaphthol 3.6 disulfo acid, especially the combination with orthotolidin in alkaline liquid, trypanblue acted more efficiently than trypanred. They further found that the azo dyestuff prepared from dichlorbenzidin and the above acid in alkaline combination—a color which produced intense staining of the tissues, and a single

injection of which caused the disappearance of the parasite—was the best agent for the treatment of nagana, mal de caderas and surra. On the other hand, a color derived from paradiaminodiphenyl-urea and the above-mentioned acid acted better than the latter color in the treatment of recurrences of the parasites, although a single injection of it never caused their complete disappearance.

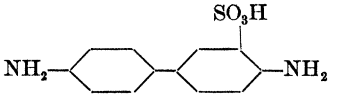
Mesnil and Nicolle then undertook some investigations on monkeys which had been inoculated with the parasite of sleeping sickness, and found that the corresponding color from paradiaminodiphenyl-urea acted best in these cases. They believed, however, that in human beings the conditions for a cure were much more unfavorable, because the patients generally came under observation at a much later period. They also proved that atoxyl was especially useful and recommended the combined use of these substances.

The following structural formulæ will give a picture of the relation of the various classes of colors employed:

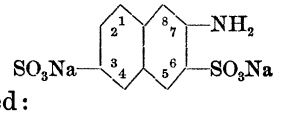
Benzidin:



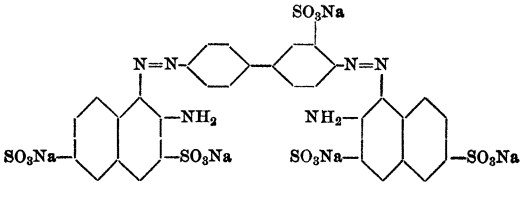
Benzidinmonosulfoacid:



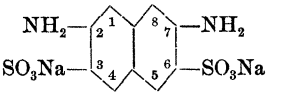
Naphthylamin disulfo acid:



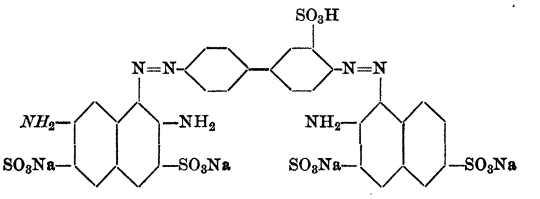
Trypanred:



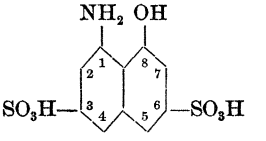
Diamidonaphthalene disulfo acid (2.7.3.6.):



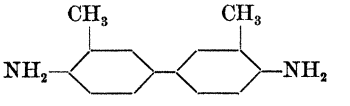
Amidotrypanred (unsymmetrical):



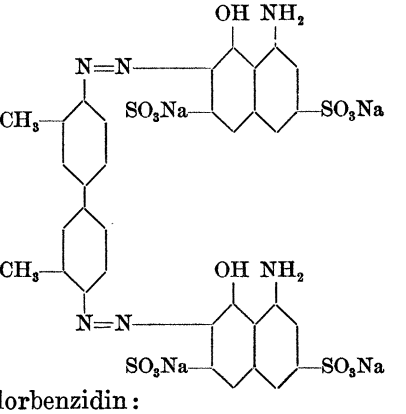
Amidonaphtholdisulfo-acid 1.8.3.6. (called Acid H):



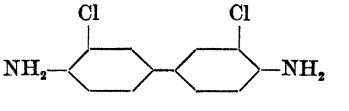
Orthotolidin:



Trypanblue:

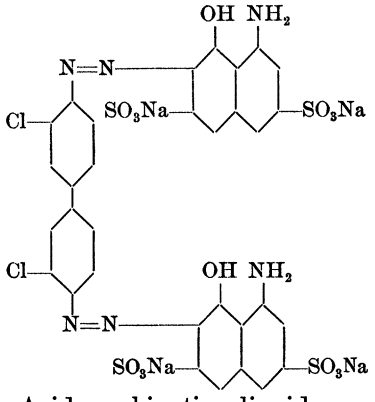


Dichlorbenzidin:

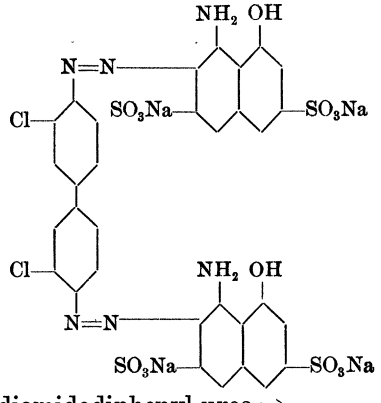


Azodyestuffs with Acid H:

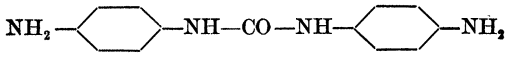
(1) Alkaline combination liquid:



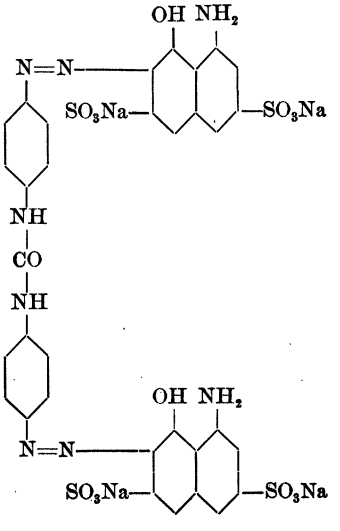
(2) Acid combination liquid:



Paradiamidodiphenyl-urea:



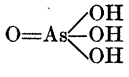
Best color against sleeping sickness:



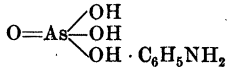
As far as it is possible to draw general conclusions from this mass of material and the results of countless investigations, Ehrlich established the rule that the effective substance must be tetrazo colors derived from naphthalene disulfo acids, with the sulfo groups in the 3.6 position. Mesnil and Nicolle determined that the effective substances must be naphthalene combinations. They must contain at least one amido group and two sulfo groups. Concerning diamines, it was found that dichlorinated substances were the best, and that those amines in which the benzol groups are connected by a two valent group (—NH—CO—NH—) were most active. The most suitable colors were those which dyed the animal body intensely, and it was shown that these were also very good cotton dyes. Altogether, symmetrical colors gave the best results and were less injurious to the health of the animals. Most of the symmetrical colors were absolutely harmless when given in such massive doses as 1 gm. for 15 to 20 gm. body weight of mice.

Concerning the chemistry of atoxyl, it may be mentioned that it is obtained by heating arsenate of anilin and treating the acid solution with alkali.

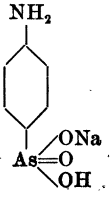
Arsenic Acid:



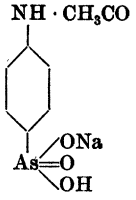
Arsenate of Anilin:



Atoxyl (P. amidophenyl arsinic acid):



Acetyl-Atoxyl:



Atoxyl contains a diazotizable NH_2 group and only one Na. It is possible to prepare azodyestuffs from atoxyl by diazotizing and combining it with the usual amines and acids, and to introduce acyl radicles into the amido group.

To Wendelstaedt belongs the credit of having shown that an entirely different class of colors is capable, even in exceedingly small doses, of causing a temporary disappearance of the trypanosomes, although possessing no definite curative action.

The chief objections to the use of these colors of the malachite- and brilliant-green group are, however, their rather injurious and irritating properties. Various attempts were made to diminish these by experimenting with derivatives of these colors.

Wendelstaedt found, as Ehrlich had previously demonstrated with various groups of chemicals—phenols, alkaloids and dyestuffs—that although sulfo derivatives were devoid of toxicity, they unfortunately lacked any destructive action upon the parasite. When Ehrlich took up experiments with the malachite-green colors he remembered from his previous experience with fuchsin colors, that by alkylation the irritating effect was materially enhanced. He therefore attributed the toxicity of malachite- and brilliant-green to the presence of the four methyl groups in the first and the four ethyl groups in the latter substance. Having previously also demonstrated that the carboxyl groups, like the sulfo groups, deprived these substances of their parasiticidal power, he concluded that by acid groups the malachite- and brilliant-green colors were, in fact, modified in the desired manner, but that the carboxyl- and sulfo-groups were too radical in their action, and that perhaps by the introduction of a faintly acid group the toxicity would be lessened without obliteration of the parasiticidal effect. As such a faintly acid group the hydroxyl group suggested itself to him, and he prepared ortho-, meta- and para-oxy-malachite-green, the di- and tri-oxy-malachite-green, and found, indeed, that they were less toxic than malachite-green, retaining, however, strong parasiticidal action. By combining some of the hydroxyl derivatives of malachite green with the trypanred treatment he succeeded in curing nagana infection when trypanred alone only prolonged life.

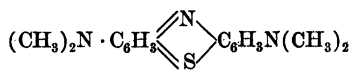
Ehrlich tried all kinds of rosanilin derivatives from the most complicated form of ortho-tri-oxy-hexa-methylpararosanilin down to the simplest pararosanilin (parafuchsin), and found that the latter best served his purpose. He therefore made all future experiments with this substance. In reviewing his tests he came to the conclusion that the best results were obtained when he fed mice for two days with cake containing parafuchsin, and then inoculated them with trypanosoma. This treatment caused the disappearance of the parasites of nagana, dourine and caderas for seven to twelve days, and proved superior to injections, which caused considerable irritation of the skin. As the mice, however, refused to eat cake impregnated with parafuchsin, it was found necessary to convert it into a difficultly soluble salt, such as the oleate with an excess of oleic acid. Some mice could be fed in this way for months without any impairment of health. If the infection was intense the feeding was preceded by an injection of fuchsin or atoxyl.

This feeding method seemed also most suitable for human beings, as injections would be too painful, 1 gm. fuchsin base daily being considered a proper initial dose. In giving parafuchsin internally it was suggested that the dose should be as large as possible, and that this treatment might be combined with the administration of atoxyl or some other drug. Ehrlich further proposed feeding with fuchsin as a preventative measure for people traveling through regions where sleeping sickness prevails.

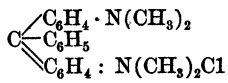
More recently most excellent results were obtained by employing instead of the above parafuchsin, chlorinated parafuchsin, which is known as "tryparosan."

The following formulæ will facilitate a review of the colors experimented upon by Ehrlich:

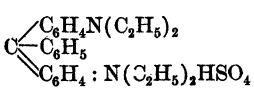
Methylenblue:



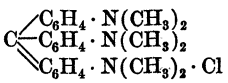
Malachitegreen:



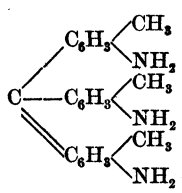
Brilliant-green:



Hexamethylviolet (completely substituted) (Crystalviolet):

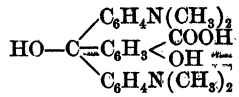


Tritolylrosanilin (New fuchsin):

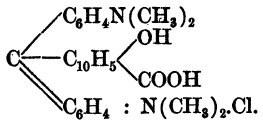


Carboxyl derivatives:

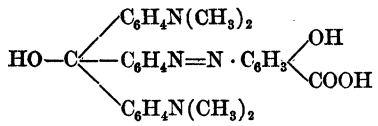
1. Chrome violet:



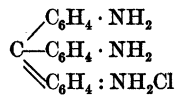
2. Chromeblue:



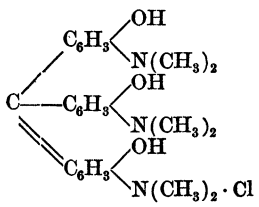
3. Azogreen:



4. Pararosanilin (parafuchsin):



5. Ortho-tri-oxy-hexa-methylpara-rosanilin:



Besides these colors Ehrlich investigated representatives of other groups of coal-tar colors, but found them inferior to those described.

The amount of work done by him can hardly be realized. It must be considered that many of the colors used had to be synthetized, as they were not commercial articles; they had then to be tested for toxicity on various species of animals, and finally their effect on trypanosoma had to be established. Of the immense material investigated only about ten substances stood the test.

There can be no doubt that thus far atoxyl has proved the most effective remedy for sleeping sickness, as it frequently causes marked improvement even

in severe cases of this disease. It is difficult to say, however, whether it is a true curative agent, since the disease is apt to run a prolonged and insidious course, and a long time, therefore, is required to judge whether a patient is actually cured. Much also depends upon the virulence of the parasite; thus, for instance, Ehrlich, who experimented with a particularly virulent strain of nagana trypanosoma, found it more refractory to atoxyl than other forms of this parasite. In this series of experiments he made the very interesting observation that acetylparaaminophenyl arsinic acid acted even better than atoxyl and proved less poisonous to mice. On the other hand, this substance was far more poisonous in other animals, such as guinea pigs or horses. Curious to say, the administration of acetylparaamidophenyl arsinic acid made "dancing mice" of the treated animals.

From these experiments the conclusion may be drawn that every species of animal and every form of trypanosoma would probably require some special curative agent, a fact which naturally makes the treatment of all the different trypanosoma affections far more difficult.

Like the parasite of relapsing fever, the trypanosoma may disappear from the blood under continued treatment, only to reappear at a later period when the disease is regarded as cured. There is thus a period of what may be termed immunity which may be of varying duration. Ehrlich found, for instance, that when mice inoculated with the trypanosoma of caderas were treated with trypanred the parasites apparently vanished completely from the blood, but in the course of twenty to thirty days reappeared and speedily caused death unless another course of treatment was substituted. Mesnil and Nicolle observed such a reappearance of the parasite after an interval of freedom of three to five months. It will be readily seen, therefore, that the disappearance of the trypanosoma in a case of sleeping sickness does not by any means signify that the patient is definitely cured. The blood has to be reexamined from time to time over long periods until an actual cure is assured. But even these tests are not absolutely positive, for it has been repeatedly shown that when the trypanosoma is no longer present in the blood and cerebrospinal fluid it may still be found in the bone marrow. Another curious circumstance is that an infected animal or human being apparently rid of the parasite and entirely well, may still be capable of transmitting the disease to others.

A further obstacle in the treatment of sleeping sickness and other trypanosoma affections is that the parasites after a time acquire a power of resisting the remedy used for their destruction. This is somewhat like the tolerance to drugs acquired by human beings. Thus, for instance, it has been found that the nagana trypanosoma when inoculated into mice could be made to disappear under treatment with fuchsin for a number of weeks, and upon their return could again be made to vanish by the same treatment. Finally, however, a time comes when this can no longer be accomplished. Evidently some change has taken place in the trypanosomes which enables them to resist what had previously proved destructive.

Browning thus has obtained strains of trypanosoma which have become resistant to the two groups of atoxyl, and to trypanblue, trypanred, etc., or even to three of these groups of substances. His researches show that this quality if once acquired is quite persistent and may even be transmitted to the progeny of the trypanosome. He believes that

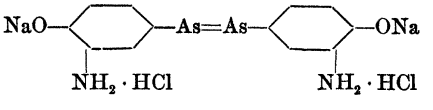
resistance to one parasiticide is true of other compounds of the same group, so that a strain of trypanosome resistant to trypanblue will also be resistant to trypanred—substances belonging to the same group, although otherwise differing widely chemically. It is a fortunate fact, however, that the parasite may still be successfully attacked by compounds belonging to other chemical groups. Probably the Ehrlich side-chain reaction best explains the mode of action of the various remedies used in the treatment of trypanosome diseases. According to this theory, the trypanosome, like a simple cell, contains various atom groups, the so-called chemoreceptors, which enter into a chemical relationship with the germicide. In the case of germicides belonging to the same class, like trypanred and trypanblue, the same atom group of the cell is attacked, while other atom groups react with other classes of antiparasitic agents, as for instance, atoxyl, parafuchsin, etc.

This theory also gives a clue in the treatment of trypanosome diseases, since it shows that instead of attacking simply one atom group of the parasite with substances with which it will enter into chemical relationship it is better to attack simultaneously several atom groups. It is like storming a fortress from various points instead of attacking one point alone.

As shown by Ehrlich, the effect of the atoxyl treatment may be increased by the simultaneous administration of trypanred, trypanblue, or fuchsin, and by such combinations it may be possible to achieve the essential aim, which is to rid the organism of the parasites in the shortest possible time.

While these investigations were going on, Uhlenhuth and Salmon published some brilliant successes obtained with atoxyl in the treatment of syphilis. Unfortunately, however, several cases of blindness were reported from the use of this remedy. The results achieved, however, were so promising that Ehrlich took up with renewed vigor the fight against the spirochete of syphilis with arsenical preparations. Soon atoxyl was replaced by arsacetin, the above-mentioned acetyl derivative of atoxyl, with even greater success, but without complete elimination of dangerous after-effects.

The constitution of atoxyl, elucidated by Ehrlich, and that of arsacetin permitted of a great variety of substitutions, and innumerable arsenic derivatives were synthetized and tested as to their effectiveness in the destruction of the spirochetes and as to their degree of toxicity upon the animal body, the object in view being that in the doses required to kill the parasite they must be free from any poisonous action upon the patient. The culmination of this long series of experiments is the wonderful Ehrlich-Hata 606, which is chemically p.p. dioxy m.m. diamido arsenobenzol in the form of the hydrochloride of its sodium salt:



A perusal of the publications appearing in the medical press on the use of this remedy is like reading tales from wonderland. With a remarkable unanimity it is stated that in less than no time the manifestations of the disease disappear, and that a condition of well being soon follows. During the 14 months of medical investigation of the drug, about fifteen thousand cases having been reported to Ehrlich, no ill-effects traceable to its use when properly administered have been observed. As reported at a meeting in Frankfort a.M., at which Ehrlich was present, two hundred

patients who were at the threshold of death had been saved from the grave by one injection.

But not only the spirochete of syphilis has been successfully attacked with this remedy, but also the spirillum of relapsing fever.

The wonderful effect of 606 and the hopes that can be entertained as to its ultimate field of utility are perhaps best illustrated by the following report of a case, published by Dr. K. Taege in the *Münchener med. Wochenschrift,* p. 1725.

The mother became infected with syphilis during pregnancy, and the child, when born, presented all the characteristic symptoms of the disease in a milder degree. It was decided to try the new treatment on the mother in the hope that the child might also obtain sufficient of the remedy through the breast milk to participate in the cure. Strange to relate, in both mother and child an improvement began to set in the third day after the injection of the drug, and as early as the fifth day all signs of the disease had almost completely vanished, and the child was practically restored to perfect health and vigor.

Of course, the author was at first inclined to believe that this marvelous effect had been brought about by the transmission of a certain amount of 606 in the milk or perhaps through the agency of arsenous acid split off from the combination; but this proved entirely erroneous, for examination of the milk with the Marsh test failed to reveal any sign of organic arsenic, while decomposition of the milk with HCl and $KClO_3$ gave only traces of inorganic arsenic.

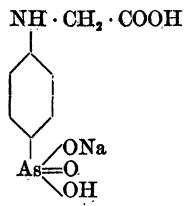
On appealing to Professor Ehrlich for an explanation, he ventured the opinion that the sudden destruction of the spirochete in the mother might have set free a large amount of toxic matter from the dead parasites, and that this in turn led to the production of antibodies by the cells, which, when transmitted through the milk, exerted the curative effect upon the child.

What an immense difference between the present-day theories and treatment and those in vogue towards the end of the year 1496 as described in a letter of the Duchess Beatrice of Milan to her sister Isabelle, Duchess of Mantua, whose husband suffered from the "French disease," as syphilis was then called. Beatrice had been asked for the loan of the services of Leonardo da Vinci, the famous painter, sculptor, mechanical engineer and inventor of flying machines, but her husband would not part with his artist friend and to sweeten the refusal, Beatrice gives her the following advice at the end of the letter: "I send your illustrious husband, Signore Francesco, a recipe against the French disease, which has been devised by our body physician, Luigi Marliani. It is claimed that it helps. The mercury inunction must be applied in the morning on an empty stomach on the uneven days of the month after the new moon. I have heard that this disease has no other cause than the fatal meeting of some certain planets, especially Mars and Venus."

To return to the subject, a marked activity in this branch of synthetic chemistry soon followed these experimental studies of arsenical preparations. Thus arsenic was produced in its colloidal form by the reduction of arsenic compounds by means of pyrocatechin, amidophenol, etc., in the presence of albumen. An arsenic proteid was obtained by the action of arsenic trichloride on vegetable albumen free from nuclein. This arsenic compound passes unchanged through the stomach and is decomposed only on reaching the intestine.

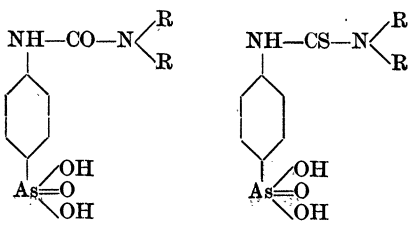
Atoxyl, or paraaminophenylarsinic acid, now called arsanilic acid, has been con-

verted into glycines by the action of chloracetic acid:



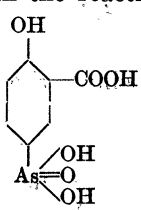
All kinds of azo and polyazo derivatives were obtained by diazotizing atoxyl and combining with the usual coupling substances, and the amido group was converted by diazotization into the oxy group or substituted by halogen.

Urea and thio-urea compounds were made from atoxyl, and substances of the following composition were obtained:

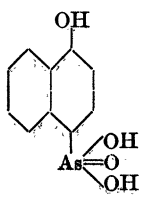


Besides the paraamido compound, the metaamido combination has been produced and employed for the various syntheses.

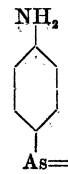
An arsinosalicylic acid has been obtained by resorting to anthranilic acid instead of anilin in the reaction



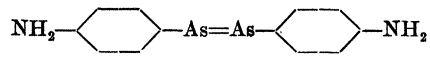
and by the use of alpha naphthylamin an alpha naphthol arsinic acid was produced



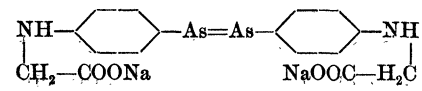
By various forms of reduction Ehrlich obtained from atoxyl a product called p. aminophenylarseneoxid



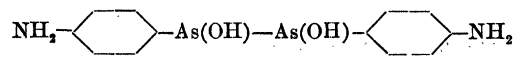
and diaminoarsenobenzol



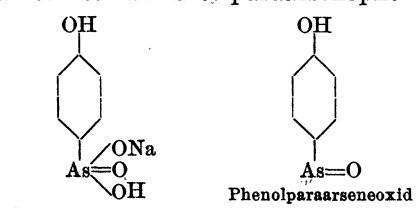
A derivative of the latter substance is spirarsyl of the formula:



By reduction with sodium amalgam diaminodihydroarsenobenzol is obtained



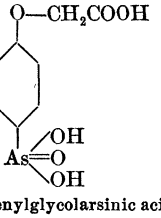
From oxyphenylarsinic acid, which is produced by heating phenol with arsenic acid, phenolparaarseneoxid is obtained by reduction, which upon treatment with hydrosulfite furnishes paraarsenophenol



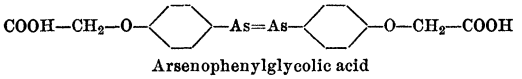
"606" is also a derivative of oxyphenylarsinic acid, and is produced from it by nitrating and reducing the thus obtained nitrooxyphenylarsinic acid to the amidooxyphenylarsinic acid. By treatment with weak reducing agents this substance furnishes the "606" preparation. As the formula shows, the product contains two atoms of trivalent arsenic, that is, the un-

stable form in contradistinction to the stable pentavalent form, in which arsenic occurs in atoxyl, arsacetin and the cacodylates. Owing to the presence of the two hydroxyl groups the product possesses acid character, enabling it to form weak salts with bases, and owing to the presence of the two amido groups it also has basic character, enabling it to form salts with acids. But either form of salt is of necessity unstable, which makes the administration of the new product a difficult one. The hydrochloride when dissolved in water is decomposed and liberates hydrochloric acid, which causes great pain when injected into the body. The practise at the present time is therefore to add enough alkali to the solution to neutralize the free acid, by which treatment the free base is precipitated and is then injected in the form of a suspension.

From oxyarylarsinic acids we obtain by condensation with chloracetic acid arylglycol arsinic acids, which upon reduction furnish arsenoarylglycolic acid

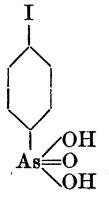


Phenylglycolarsinic acid

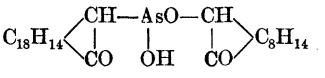


Arsenophenylglycolic acid

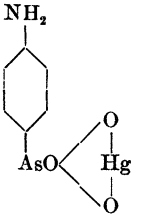
Among other substitution products we must mention an iodin derivative, the p.iodinphenylarsinic acid and its diiodide:



and a camphor combination, the dicamphorarylarsinic acid, obtained by the action of arsenictrichloride upon sodium camphor:



An interesting combination of the mercury treatment hitherto in use with the new method by means of the arsenic preparations is represented by the synthesis of the atoxylate of mercury



with which Uhlenhuth, the originator of the substance, has obtained excellent results.

If, after all that has been stated above, we now define chemotherapy, it can perhaps best be described as the science dealing with the treatment of internal parasitic diseases by means of preparations synthetized with the object of combining the maximum power of efficiency in the destruction of the greatest variety of protozoa with the minimum poisonous action upon the patient's tissues, this combination of properties being primarily established by animal experimentation.

In contradistinction to chemotherapy, serumtherapy is the method of treating bacterial infections by means of antibodies generated by the diseased organism itself.

If, as seems improbable from the brilliant results reported in such abundance by many of the greatest authorities in the medical world, the new remedy should suffer a setback through later observations of serious after-effects, it would not detract in the least from the magnificent

services which Ehrlich and his pupils have rendered humanity. Such vast progress has already been achieved in chemotherapy that it will necessarily be only a matter of a short time when it will become possible to definitely arrest the ravages of such terrible diseases as syphilis, recurrent fever and sleeping sickness. Perhaps cancer, the cause of which has been ascribed by some investigators to organisms resembling the spirochete of syphilis, will also be found amenable to chemotherapy.

This marvelous success of modern therapy is, in a large measure, due to synthetic chemistry, which in the past has already rendered invaluable assistance to the medical practitioner by furnishing him such efficient remedies as antipyrin, phenacetin, trional, veronal, hexamethylen-tetramin, and aspirin. How, in the light of these positive advances, can we explain the attitude of those few who are still opposed to progress in medicine to which our science has chiefly contributed. A few years ago when we celebrated the birth of synthetic chemistry by commemorating the fiftieth anniversary of Perkin's discovery of the first anilin color, one of these obstructionists stated in a discussion that he believed very few useful drugs had been put out by the manufacturing chemists, and that we should be better off if Perkin had never discovered coal-tar products. The anilin colors were cheap and gaudy and did not last, and the coal-tar drugs were in the same class. He believed that the good that coal-tar products had done was being neutralized by the harm.

Let us hope that after a closer study of the subject this short-sighted man has meanwhile learned that he is wrong in every particular; for there exist coal-tar dyes which are ever so much faster than any coloring matter supplied by nature, and coal-tar derivatives in the hands of competent physicians do as little harm as any active drug in the pharmacopœia.

In fact, it is no exaggeration to say that there is scarcely a department in medicine that has not directly benefited through the discovery of the coal-tar products and especially of the anilin dyes. It has provided the anatomist and pathologist with the means of staining various tissues and thus of studying not only their normal structure but the alterations caused by disease. It is the foundation upon which has been built the modern science of bacteriology, enabling the investigator in this field to distinguish between the different disease organisms and to determine their presence by various tests, and now it bids fair to equip the physician with the most potent weapons in the warfare against disease.

H. SCHWEITZER

NEW YORK CITY

THE INSTRUCTION OF LARGE UNIVERSITY CLASSES

THE great increase of students in universities has brought up the problem of instructing students efficiently in large classes. The problem presents so many difficulties, and is one that so many instructors are wrestling with, that we have thought that it might be of value to describe the methods of handling large classes in a physics course in which there are lectures, recitations and laboratory exercises.

In this course there are registered about 400 students. Two lectures are given each week together with one quiz and two two-hour laboratory periods. The course continues throughout the college year, and covers the usual range of topics of a course in general physics. The lectures are given on Monday and Wednesday mornings at nine o'clock and repeated at eleven o'clock on the same days, the class being divided equally for the two periods. Experience has shown that 200 is a maximum number of students for experimental lectures, even with a good lecture