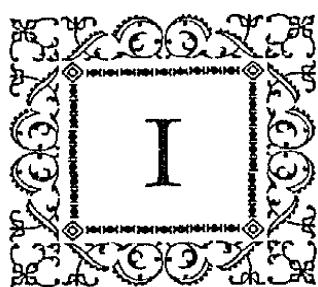


The Theoretical Basis of Paul Ehrlich's Chemotherapy

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IN spite of all that has been written about Paul Ehrlich (1854–1915), especially with respect to his work in chemotherapy, an understanding of his ideas and contributions is far from satisfactory.¹ My aim in this paper is to analyze in detail one important aspect of Ehrlich's thought, the theoretical basis of his chemotherapy.

Paul Ehrlich is generally acknowledged to be the founder of modern chemotherapy. What did Ehrlich mean by the term *chemotherapy*, which was introduced into medicine through his work?² Chemical substances

1. The bibliography of secondary sources in the article on Paul Ehrlich by Claude Dolman in the *Dictionary of scientific biography*, which makes no claim to completeness, contains some sixty-five references. Ehrlich's contributions have received a significant amount of attention in the popular literature (and even in a Hollywood motion picture), but such accounts are generally superficial and often inaccurate. Even more serious studies of Ehrlich, however, have failed to provide an in-depth historical analysis of the development of his scientific work. The article by Dolman is useful, but provides only a relatively brief overview of Ehrlich's life and work. The few existing book-length biographies are undocumented and inadequate. The biography by his secretary, Martha Marquardt, *Paul Ehrlich* (London, 1949), gives a vivid picture of Ehrlich's personality, but treats his scientific work in a disjointed and superficial manner. Professor James Hirsch of the Rockefeller University is studying the Ehrlich manuscript materials with the goal of providing a biographical study emphasizing Ehrlich's scientific contributions.

2. Ehrlich is generally credited with having coined the term *chemotherapy*. See H. A. Skinner, *The origin of medical terms*, 2nd ed. (Baltimore, 1961), p. 103; and Henry Wain, *The story behind the word: some interesting origins of medical terms* (Springfield, Ill., 1958), p. 65. The term certainly is associated with Ehrlich's name in the literature of the early twentieth century, and there can be little doubt that it entered the medical vocabulary through his work, but it is possible that someone may have used the word earlier. Ehrlich's earliest use of the word *chemotherapy* (*Chemotherapie*), as far as I know, was in his 'Address delivered at the dedication of the Georg-Speyer Haus' on 6 September 1906, but not published until 1960 in *The collected papers of Paul Ehrlich*, ed. F. Himmelweit, 3 vols. (London, 1956–60), III, 53–63. His earliest published use of the term appears to have been in 1907 in his 'Chemotherapeutische Trypanosomen-Studien,' *ibid.*, pp. 81–105 (*Berl. klin. Wschr.*, 1907, 44, 233–236, 280–282, 310–314, 341–344).

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had been used in therapeutics long before Ehrlich's time. Sometimes Ehrlich appears to have used the term in a general sense to refer simply to the use of chemicals in therapy, as when he stated that '. . . from the very origin of the art of healing, chemotherapy has been in existence, since almost all of the medicaments that we employ are chemical.'³ Usually, however, he had a much more specific and limited use in mind, and he often qualified the term with the adjectives *specific* or *experimental*. Pharmacologist Hans Herken has recently argued: 'The term "chemotherapy" introduced by Paul Ehrlich is incomplete without the adjective "specifica" which was also added by him.'⁴ Chemotherapy in this sense meant to Ehrlich the use of chemical substances, especially those produced synthetically, to destroy pathogenic microorganisms within the body. Ehrlich expressed the task of his institute of chemotherapy at the Georg-Speyer-Haus in Frankfurt as follows:

Here we shall . . . be concerned with the problem of curing organisms infected by certain parasites in such a way that the parasites are exterminated within the living organism, so that the organism is disinfected . . . by the use of substances which have had their origin in the chemist's retort. Thus, the task of the new institute will be a *specific chemotherapy of infectious diseases*.⁵

Ehrlich generally used the term *chemotherapy* in this sense. Chemotherapy, as he saw it, was a part of the broader field of experimental therapeutics, a field he differentiated clearly from pharmacology. The science of pharmacology had emerged as a separate discipline in the nineteenth century under the guidance of such men as Rudolf Buchheim and especially Oswald Schmiedeberg, a contemporary of Ehrlich's and the most prominent and influential pharmacologist of his time. While admitting that pharmacology had contributed significantly to our knowledge of physiology and had led to the introduction of a number of drugs that were valuable for symptomatic treatment (analgesics, antipyretics,

3. Paul Ehrlich, 'Chemotherapy,' *Collected papers* (n. 2), III, 505-518, p. 505 (International medical congress, 17th, London, 1913, *Proceedings* [London, 1914], pp. 94-111). Ehrlich went on to add that 'on the other hand, experimental chemotherapy could only develop in a fruitful manner in modern times.'

4. Hans Herkin, *Paul Ehrlich: pioneer of chemotherapy* (Berlin, n.d.), p. 8. Address delivered at the Weizmann Institute of Science, Rehovot, Israel, 25 March 1976.

5. Ehrlich, 'Address' (n. 2), p. 60. For similar expressions of this definition of specific or experimental chemotherapy see Ehrlich, 'Chemotherapeutische' (n. 2), p. 81; and Paul Ehrlich and R. Gonder, 'Experimentelle Chemotherapie,' in S. von Prowazek, ed., *Handbuch der pathogenen Protozoen*, 3 vols. (Leipzig 1912-31) II, 752-780 (*Collected papers* [n. 2], III, 559-582, p. 559). For a discussion of the problem of agreeing upon a single definition of chemotherapy since Ehrlich's time, see Glenn Sonnedecker, 'The concept of chemotherapy,' *Am. J. pharm. Ed.*, 1962, 26, 1-3.

hypnotics, etc.), Ehrlich argued that the discipline had contributed little to the discovery of 'specific (that is, truly curative) drugs.' Pharmacology had concentrated on the effects of drugs upon healthy animals, and therefore could not solve the problem of curing disease.⁶

Experimental therapeutics, Ehrlich explained, involved producing diseases experimentally in animals and then studying the action of drugs against these diseases. The infectious diseases were the easiest to reproduce in laboratory animals, and experimental therapeutics had already achieved significant progress in the development of immunological agents to control or treat certain of these diseases.⁷ Ehrlich divided experimental therapeutics into three categories: organotherapy (the use of organ extracts, or what we would call hormones), bacteriotherapy (the use of immunological agents such as antitoxins), and experimental chemotherapy, the newest and perhaps the most difficult of these fields.⁸

Ehrlich's chemotherapy was based upon the concept of selective affinity. In order for a drug to exert its effect on a pathogenic microorganism, or on any cell for that matter, it must first be fixed within the cell. In an address on chemotherapy, Ehrlich stated:

The whole field is governed by a simple, I might even say natural, principle. If the law is true in chemistry that *corpora non agunt nisi liquida*, then for chemotherapy the principle is true that *corpora non agunt nisi fixata*. When applied to the special case in point, this means that parasites are killed only by those substances for which they have a certain affinity, by virtue of which these are fixed by the parasites. I call such substances *parasitotropic*.⁹

The problem is, however, that chemicals that have an affinity for the cells of parasites are likely also to have an affinity for human cells, or in Ehrlich's terminology to be *organotropic*. Therefore one must search for therapeutic agents that are selective and that possess a relatively high affinity, and toxicity, for the parasite in relation to the animal body, so that it is possible to kill the parasites without serious damage to the body.¹⁰

The most ideal agents in this sense are the immunological products of the body because these antitoxins and antibodies exert an extremely specific action on the parasites evoking their production, and having no effect

6. Paul Ehrlich, 'Über der jetzigen Stand der Chemotherapie,' *Collected papers* (n. 2), III, 150-170, pp. 150-151 (*Ber. dt. chem. Ges.*, 1909, 42, 17-47).

7. *Ibid.*, p. 151.

8. Letter from Paul Ehrlich to A. von Rosthorn, 18 January 1907, Paul Ehrlich copybooks, Rockefeller University, New York, Ser. v, No. XXI, pp. 138-140.

9. Ehrlich (n. 3), p. 507.

10. Ehrlich (n. 6), p. 153.

on the cells of the host. These immune substances are like 'magic bullets' which seek out and destroy the enemy without harming the body. But many infectious diseases are not amenable to treatment by serum therapy; hence we must turn to chemotherapy.

In general, Ehrlich noted, chemotherapy is a more complicated task than serum therapy because chemical agents, in contrast to antibodies, are likely to be harmful to the body. It was not easy to score direct hits as with the antibodies. We must learn, Ehrlich added, to aim in a chemical sense. Ehrlich thus recognized the difficulty of obtaining perfect chemotherapeutic drugs which attacked only the microorganism and not the host.¹¹ He did not claim that Salvarsan, the most important chemotherapeutic agent that he developed, was a 'magic bullet' for therapeutic purposes in the same sense that the antitoxins were. He did hold out the hope, however, that it might be possible someday to synthesize such an ideal chemical medicament,¹² and he probably thought that Salvarsan was closer to that ideal than it actually was.¹³

Ehrlich developed an interest in the selective action of drugs and chemicals while he was still a student. The idea that drugs have a selective action was not original to Ehrlich. The fact that drugs may exert their effects on specific organs had long been recognized empirically and expressed vaguely in the traditional designation of certain remedies as cordials, hepatics, etc.¹⁴ In the late eighteenth and early nineteenth centuries, the belief that most drugs exerted their effects by acting directly on the nerves at the site of action came to dominate pharmacological thought. The theory of the action of drugs on nerves argued that selective action was more apparent than real. The theory supposed that the drug produced a generalized reaction in the body with each organ responding in its own peculiar manner. Some body responses, however, were more dominant than others, thus giving rise to an erroneous impression that the drug acted selectively only on certain organs.¹⁵

11. *Ibid.*, pp. 152-153; Paul Ehrlich, 'Über moderne Chemotherapie,' *Collected papers* (n. 2), III, 140-149, pp. 140-141 (*Verh. Kongr. dt. dermat. Ges.*, 1908, 10, 52-70).

12. Ehrlich (n. 3), p. 510.

13. See, for example, his overly optimistic statements about Salvarsan in 'Closing notes to the experimental chemotherapy of spirillooses,' *Collected papers* (n. 2), III, 282-309, especially pp. 308-309 (*Die experimentelle Chemotherapie der Spirilloesen* [Berlin, 1910], pp. 114-164).

14. M. P. Earles, 'Early theories of the mode of action of drugs and poisons,' *Ann. Sci.*, 1961, 17, 97-110, p. 98.

15. M. P. Earles, 'The action of medicines: problems of explanation in the eighteenth and early nineteenth centuries,' *International Congress of the History of Medicine, 13th, London, 1972, Proceedings*, 2 vols. (London, 1974), II, 1177-1181, pp. 1177-1178.

By 1850 the pharmacological studies of François Magendie, James Blake, and others in the first half of the nineteenth century had largely discredited the theory of action through the nerves. Most pharmacologists and physiologists had by mid-century come to accept the concept that drugs are absorbed into the bloodstream at the site of administration and must be transported by the blood to the specific organ or organs on which they act. The absorption theory emphasized the selective action of a drug at a specific site distant from the site of administration. Magendie, for example, was able to demonstrate that strychnine-containing arrow poisons acted specifically on the spinal cord.

The absorption theory raised the question of how drugs or poisons, present in the blood and in contact with all organs, might act only on one organ, leaving the others unaffected. One might attempt to offer a physicochemical explanation for this fact or one might fall back upon a vitalistic approach by assuming, as Anthony Todd Thomson did in the 1830s, that specific medicines possess 'peculiar energies' to excite an organ.¹⁶

The question of the selective action of drugs and poisons attracted Ehrlich's attention early in his career. Ehrlich recalled that while still a medical student in the early 1870s he read a work on lead poisoning by Emil Heubel which greatly impressed him.

In order to elucidate the nature of this poisoning, the author had estimated quantitatively the lead content of the liver, the kidney, and the heart and had discovered that there were remarkable differences in the amount of lead to be found in various organs. When he immersed organs of normal animals in dilute lead-solutions and subsequently subjected the organs to chemical analysis, he believed that he obtained exactly the same difference. This experiment seemed to me, at that time, a revelation. The possibility emerged that this technique might be used also to ascertain the site of action of poisons.¹⁷

That lead was to be found in certain organs, for example, the brain, was for Ehrlich only the starting point for an investigation. The brain was a complex structure made up of various tissues. Ehrlich wanted to know within which cells of the organ the poison was concentrated, but his attempts to determine the location of the poison with the aid of a microscope resulted in failure.

He became fascinated by the distribution of substances among the cells

16. *Ibid.*, pp. 1178-1179.

17. Ehrlich, 'Address' (n. 2), p. 54. The publication that Ehrlich referred to is undoubtedly Emil Huebel's *Pathogenese und Symptome der chronischen Bleivergiftung Experimentelle Untersuchungen* (Berlin, 1871).

of the body. The concept that drugs act only upon those organs that take them up was an old one, but Ehrlich felt that it had not been given sufficient emphasis in pharmacology and that it had remained only a general theoretical principle because the laws governing distribution were so little understood. He decided to investigate this *storage-axiom*, as he termed the principle.

Ehrlich began by studying the distribution of dyes in living tissues because only here could he easily determine the distribution of the substance by its color.¹⁸ His interest in dyes may well have been aroused by his cousin Carl Weigert, a pioneer in the field of histological staining. The thesis that Ehrlich presented for his graduation in medicine at the University of Leipzig in 1878 dealt with the theory and practice of histological staining. It is of interest to us here because it clearly demonstrates Ehrlich's early concern with the question of selective affinity, in this case the affinity of particular dyes for certain types of tissues, and also his commitment to a chemical viewpoint. He rejected the idea that the process of staining involved only a physical adhesion of the dye to the tissue, but believed that the interaction was of a chemical nature (probably similar to that involved in the formation of so-called *double salts*, that is, the linking together of two apparently saturated compounds such as silver chloride and mercurous oxide). Ehrlich also noted in this dissertation that he believed there were colorless substances that had similar 'sticking' properties to those of dyes.¹⁹

Ehrlich's interest in dyes continued, and his *Habilitationschrift* for his appointment as *Privatdocent* in the University of Berlin in 1885 was an investigation of the ability of various tissues to reduce certain dyestuffs. This work is important in the present context largely because it concerns the first indication of his side-chain theory of cellular action, a concept that played a very significant role in his later thinking about immunology and chemotherapy. Ehrlich adopted Eduard Pflüger's view that protoplasm may be envisioned as a giant molecule consisting of a chemical nucleus of special structure which is responsible for the specific functions of a particular cell (for example, a liver cell or a kidney cell), with attached chemical side chains. These side chains are more involved in the vital processes common to all cells, such as cellular oxidation. Some side chains, Ehrlich believed, possess the ability to fix oxygen or, more accurately, to give up hydrogen to oxygen and thus become oxidizing agents themselves. Other

18. Ehrlich, 'Address' (n. 2), pp. 54-55.

19. Paul Ehrlich, 'Contributions to the theory and practice of histological staining,' *Collected papers* (n. 2), I, 65-98, pp. 67-76 (M.D. diss., University of Leipzig, 1878).

side chains were involved in nutrition, and probably consisted of 'combustible molecule-groups' that were consumed during the process of oxidation and then regenerated.²⁰

At about this same time (1885), Ehrlich was also becoming involved in his first significant pharmacotherapeutic investigations. In the period 1885 to 1894 he published studies on the properties of various drugs, including iodine, thalline, methylene blue, and cocaine.²¹ An examination of these studies reveals that Ehrlich was continuing to develop some of the methods and concepts that were to play a part in his later work on the chemotherapy of trypanosomal diseases and syphilis. Once again we see Ehrlich's concern with selective affinity and distribution in this work.

Let us consider, for example, his investigation of methylene blue. In the course of his work on histological staining, Ehrlich reported in 1886 that methylene blue selectively stained living nerve tissue.²² The dye thus exhibited a selective affinity towards nerve tissue, or, in Ehrlich's words, it was 'neurotropic.' Ehrlich's conviction, already developing at that time, that a drug must first become fixed or stored in a cell in order to act on it led him in 1890 to try methylene blue in the clinical treatment of pain in neuralgia because of its affinity towards nerve cells.²³ The following year, stimulated by the knowledge that methylene blue is an excellent stain for plasmodia, the causative agent of malaria, Ehrlich tried the dye in the treatment of two cases of malaria in humans.²⁴ The results were promising, but since Ehrlich was working in Berlin where cases of malaria were rare, and since at that time the disease could not be reproduced experimentally in laboratory animals, he had little opportunity to follow up on this work. This study marks Ehrlich's first real foray into the chemotherapy of infectious disease and the beginning of his search for parasitotropic substances.

These early therapeutic studies also reveal Ehrlich's interest in understanding the relationship of the pharmacological activity of a drug to its chemical structure and in attempting to modify that structure to produce

20. Paul Ehrlich, 'The requirement of the organism for oxygen: an analytical study with the aid of dyes,' *Collected papers* (n. 2), I, 433-496 (*Das Sauerstoffbedürfnis des Organismus: eine farbenanalytische Studie* [Berlin, 1885]).

21. See, for example, Paul Ehrlich, 'Über Wesen und Behandlung des Jodismus,' *Collected papers* (n. 2), I, 530-534 (*Charité-Ann.*, 1885, 10, 129-135); and idem, 'Experimentelles und Klinisches über Thallin,' *Collected papers* (n. 2), I, 542-551 (*Dt. med. Wschr.*, 1886, 12, 849-851).

22. Paul Ehrlich, 'Über die Methylenblaureaction der lebenden Nerven-substanz,' *Collected papers* (n. 2), I, 500-508 (*Dt. med. Wschr.*, 1886, 12, 49-52).

23. Paul Ehrlich and A. Leppman, 'Über schmerzstillende Wirkung des Methylenblau,' *Collected papers* (n. 2), I, 555-558 (*Dt. med. Wschr.*, 1890, 16, 493-494).

24. P. Guttmann and Paul Ehrlich, 'On the action of methylene blue on malaria,' *Collected papers* (n. 2), III, 15-20 (*Berl. klin. Wschr.*, 1891, 28, 953-956).

desired changes in activity, again foreshadowing his later chemotherapeutic work with azo dyes and arsenicals. Ehrlich was by no means the first to study the relationship between structure and activity, a subject that had been pioneered by British scientists such as James Blake, Benjamin Ward Richardson, Alexander Crum Brown, and Thomas Fraser in the period from about 1840 to 1870.²⁵ But Ehrlich was eventually to utilize structure-activity considerations in a sustained and systematic way in the first successful synthesis of a significantly effective chemotherapeutic agent, namely, Salvarsan.

Working with Alfred Einhorn in the early 1890s, Ehrlich investigated the properties of cocaine and various related compounds and determined that the benzoic acid radical was the portion of the molecule responsible for anesthetic action or, as Ehrlich phrased it, was the 'anesthesiophore group' of the molecule.²⁶ The chemical constitution of the drug molecule was also important in determining the distribution of the substance in the body. Ehrlich tended to attribute the specific therapeutic action of a drug (such as anesthetic properties) to the presence of a particular functional group, whereas he felt that the distribution of the drug depended upon the entire constitution or structure. In 1898 he expressed his conception of the best approach to the synthesis of pharmacologically active agents: 'If one is desirous of studying organ therapy in this sense, it is first of all necessary to seek for substances which possess a particular affinity for a certain organ. Having found such substances, one could then use them, so to speak, as a vehicle, with which to bring therapeutically active groups to the organ in question.'²⁷ Ehrlich's later conception of the search for chemotherapeutic agents was basically similar, except that the emphasis was on finding substances that had a particular affinity for a pathogenic microorganism rather than for a specific organ within the human body.

In the 1890s, however, Ehrlich's attention was largely diverted from synthetic chemical drugs to the newly emerging field of immunological therapy. In 1890 he was provided with laboratory space in Robert Koch's newly founded Institute for Infectious Diseases at Berlin and became actively involved in immunological work. Emil von Behring's discovery of

25. See John Parascandola, 'Structure-activity relationships: the early mirage,' *Pharm. Hist.*, 1971, 13, 3-10. Cf. William F. Bynum, 'Chemical structure and pharmacological action: a chapter in the history of 19th century molecular pharmacology,' *Bull. Hist. Med.*, 1970, 44, 518-538.

26. Paul Ehrlich and A. Einhorn, 'Über die physiologische Wirkung der Verbindungen der Cocainreihe,' *Collected papers* (n. 2), 1, 567-569 (*Ber. dt. chem. Ges.*, 1894, 27, 1870-1873).

27. Paul Ehrlich, 'The relations existing between chemical constitution, distribution and pharmacological action,' *Collected papers* (n. 2), 1, 596-618, p. 618 (*Ernst von Leyden Festschrift* [Berlin, 1902], pp. 647-679).

diphtheria antitoxin at Koch's institute in late 1890, with Ehrlich's later important role in helping to develop a sufficiently potent and standardized preparation for therapeutic use, stimulated great interest in serum therapy.²⁸ Although Ehrlich's contributions to immunology, which were significant enough to merit the Nobel Prize in 1909, are beyond the scope of this paper, we must consider at least briefly his famous side-chain theory of immunity because of its later influence on his concept of chemotherapy.

In 1897, to explain the process of immunization, Ehrlich called upon the side-chain theory which he had used earlier to explain cellular oxidation. Assume, he postulated, that one of the side chains (or *receptors*, as he later also referred to them) of the cell possesses an atom group with a specific combining property for a particular toxin, such as tetanus toxin. This side chain is normally involved in ordinary physiological processes, such as nutrition, and it is merely coincidental that it has the ability to combine with tetanus toxin. Combination with the toxin, however, renders the side chain incapable of performing its normal physiological function. The cell then produced more of these side chains to make up for the deficiency, but it overcompensates so that excess side chains are produced, break away from the cell, and are released into the bloodstream. These excess side chains in the blood are what we call antibodies or antitoxins. They neutralize the toxin by combining with it, thus preventing it from anchoring itself to the cell and exerting its poisonous effects.²⁹

Ehrlich went on to distinguish between what he called the *toxophore* and the *haptophore* groups of the toxin. The *haptophore* group is the atom group involved in binding the toxin to the side chain. Once the toxin is thus anchored to the cell, the cell comes under the influence of the *toxophore* group, which is responsible for the poisonous properties of the toxin.³⁰ He may well have derived this concept from an analogy with

28. On Ehrlich's role in the development of the diphtheria antitoxin see Dolman (n. 1) and Marquardt, *Ehrlich* (n. 1), pp. 29-40.

29. Paul Ehrlich, 'The assay of the activity of diphtheria-curative serum and its theoretical basis,' *Collected papers* (n. 2), II, 107-125, pp. 113-115 (*Klin. Jb.*, 1897, 6, 299-326). He referred in this paper (p. 115) to 'receptive side chains,' but did not use the term *receptor* until 1900. See Paul Ehrlich, 'On haemolysins: third communication,' *ibid.*, pp. 205-212, especially p. 205 (*Berl. klin. Wschr.*, 1900, 37, 453-458). For more detailed discussions of Ehrlich's immunological theory, see Pauline Mazumdar, 'The antigen-antibody reaction and the physics and chemistry of life,' *Bull. Hist. Med.*, 1974, 48, 1-21; and Lewis P. Rubin, 'Styles in scientific explanation: Paul Ehrlich and Svante Arrhenius on immunochemistry,' *J. Hist. Med.*, 1980, 35, 397-425.

30. In his first paper on the side-chain theory Ehrlich differentiated between the binding group and the toxic group of the toxin, using the terms *combining group* and *toxophore group*, respectively. See his 'Diphtheria-curative serum' (n. 29), pp. 113-117. He introduced the term *haptophore* for the combining group the very next year. See Paul Ehrlich, 'Über die Constitution des Diphtheriegiftes,' *Collected papers* (n. 2), II, 126-133, p. 131 (*Dt. med. Wschr.*, 1898, 24, 597-600). For a more elaborate

dyes, in which the chemical grouping responsible for color is different from that responsible for fixing the dye to the fabric or tissue.

Ehrlich's theory became more elaborate as he struggled to explain various immunological phenomena, but we need not consider these modifications for our present purposes. I have outlined Ehrlich's side-chain theory of immunity because this concept was later to play a key role in his theory of chemotherapy. It must be stressed, however, that Ehrlich did not immediately apply the side-chain theory to the question of drug action. In fact, he did not do so for some ten years, and at first he specifically denied that drugs were bound to the cell in a manner similar to the binding of toxins, a fact that is generally overlooked in accounts of Ehrlich's work.

The reason for Ehrlich's reluctance to apply the side-chain concept to drugs derived from the observations that many drugs can be easily extracted from tissues by solvents and that the action of many drugs is of a transitory character. Therefore, chemical drugs could not be bound firmly by the cell in the manner of toxins because they were not incorporated into the protoplasmic molecule by a chemical union. They did not possess haptophore groups and were not capable of evoking the production of antibodies.

Yet Ehrlich was well aware that drugs exhibit a selectivity for certain tissues. How then did he explain this specificity if not on the basis of his side-chain or receptor concept? It is not surprising that Ehrlich again drew upon his experience with dyes in explaining the specificity of drug action. As noted earlier, he believed that the fixing of dyes was not simply a physical or mechanical process involving surface attraction and adsorption. He discussed two current theories of the mechanism of action of dyeing or staining, each of which he felt might be correct in certain cases. The first of these involved the combination of the dye with a constituent of the fabric to form an insoluble, salt-like compound called a *lake*. A similar process might occur, he believed, in the tissues of the organism in the case of drugs, with a drug combining with a free substance (such as an acid) in the cell to form an insoluble compound that precipitates out of solution and is thus fixed in the cell. Cells that possessed constituents capable of forming a lake with a particular drug could thus localize that drug. The second theory of dyeing discussed by Ehrlich involved the formation of

summary of his theory of immunity, see Paul Ehrlich, 'On immunity with special reference to cell life,' *Collected papers* (n. 2), II, 178-195 (*Proc. roy. Soc. Lond.*, 1900, 66, 424-448).

solid solutions in which the dye forms a homogeneous mixture with the substance of the fabric. He suggested that some drugs might be fixed in cells through a similar process, by being dissolved in the fat-like substances of certain tissues. Note that both of these mechanisms are different from the side-chain theory and do not involve combination of the drug with a receptor in the cell, although Ehrlich did note that they both involved 'chemical affinities in the widest meaning of the term.'³¹

Ehrlich's doubt about the probability of a true chemical combination taking place between the drug and the cell were shared by many of his contemporaries. Chemical combination was generally thought of at the time essentially in terms of what we would call covalent or ionic bonds, which are not easily broken. Such concepts as hydrogen bonds and Van der Waals bonds had not yet been developed. It was thus hard to reconcile phenomena such as the ease with which many drugs could be washed out of tissues by solvents with the contemporary concepts of chemical bonding. Many pharmacologists leaned towards the view that drugs often induce their effects through their physical properties, by altering the surface tension, electrolytic balance, osmotic pressure, etc., of the cell, rather than through the formation of chemical bonds with protoplasmic constituents.³²

Ehrlich was to change his mind about the mechanism of action of drugs, however, as he became deeply involved in chemotherapeutic studies, and the receptor or side-chain theory was to come to form the theoretical basis of his chemotherapy. By 1898 Ehrlich was once again involved with therapeutic researches with dyes, and by 1903 he and his coworkers had begun an extensive series of chemotherapeutic investigations at the Institute for Experimental Therapy in Frankfort.³³ In 1906 Ehrlich was provided with additional space and funds for these studies when the Georg-Speyer-Haus for Chemotherapy, financed by Frau Franziska Speyer in memory of her late husband, was built adjoining the Institute for Experimental Therapy. From that time on, he turned his attention more and more away from immunology and towards chemotherapy. At the time that the Speyer-Haus was being planned, he wrote to a friend that he felt he had exhausted the

31. See John Parascandola and Ronald Jasensky, 'Origins of the receptor theory of drug action.' *Bull. Hist. Med.*, 1974, 48, 199-220, pp. 205-209. See also Ehrlich (n. 27), pp. 608-616.

32. See John Parascandola, 'The controversy over structure-activity relationships in the early 20th century,' *Pharm. Hist.*, 1974, 16, 54-63.

33. James G. Hirsch, 'The conquest of bacterial infectious diseases in the twentieth century: the greatest success story in the history of medical sciences,' Ms. Professor Hirsch notes that the Ehrlich copybooks provide evidence that by 1898 Ehrlich had set out to find a derivative of methylene blue that would have a better therapeutic index.

field of immunity and was pleased to have the opportunity to cultivate chemical therapy, which had always been his favorite field, in the proper way.³⁴

In 1900 only a few drugs were available that actually combatted the causes of infectious diseases, that is, pathogenic microorganisms, and these had largely been discovered empirically. Quinine was perhaps the most prominent example of such a curative drug. The many new synthetic drugs developed in the late nineteenth century (such as phenacetin and aspirin) all tended to treat symptoms rather than causes of disease. They were antipyretics, analgesics, sedatives, etc. A number of chemical disinfectants such as carbolic acid did exist, but they were too toxic for use within the body. Efforts were made to find disinfectants that might be used internally, but the results were discouraging.³⁵ Little progress had been made in the nineteenth century towards developing the specific antimicrobial drugs that Ehrlich had in mind.

A rational, systematic search for specific chemotherapeutic agents against various infectious diseases could not have been carried out before the germ theory of disease was established in the latter part of the nineteenth century, and before methods had been developed for the identification, isolation, and culture of pathogenic microorganisms. Research in experimental therapeutics, as Ehrlich called it, was hampered also by the difficulty of reproducing certain human diseases in experimental animals (as in malaria).

Ehrlich and his coworkers began investigating the effects of various chemicals in the treatment of trypanosome infections in experimental animals, and, not surprisingly, their attention at first was concentrated on dyes. Many of the compounds tested were received through Dr. Arthur Weinberg, director of the Cassella and Company Dye Works near Frankfurt.³⁶ Ehrlich found that dyes in the benzopurpurin series seemed the most promising of the compounds then under investigation, and by the addition of a sulfonic acid group to one of these dyes, to increase solubility, trypan red was prepared. This red dye seemed to cure mice with trypanosome infections completely, but unfortunately it was ineffective in rats and larger animals.³⁷

34. Letter from Paul Ehrlich to Leopold Landau, 8 February 1905, Ehrlich copybooks (n. 8), Ser. v, No. xvi, pp. 26-28.

35. For a discussion of efforts to find 'internal disinfectants' in the nineteenth century, see John Crellin, 'Internal antiseptics or the dawn of chemotherapy?' *J. Hist. Med.*, 1981, 36, 9-18.

36. Marquardt, *Ehrlich* (n. 1), p. 121. See also the correspondence between Ehrlich and Weinberg in the Ehrlich copybooks (n. 8) from this period.

37. Paul Ehrlich and K. Shiga, 'Farbentherapeutische Versuche bei Trypanosomenkrankung,' *Collected papers* (n. 2), III, 24-29 (*Berl. klin. Wschr.*, 1904); Ehrlich, 'Address' (n. 2), pp. 61-63.

Arsenic compounds also attracted the attention of Ehrlich's group. Arsenic had been used to some extent therapeutically in the treatment of certain trypanosomal diseases even before the microorganism had been identified as the cause.³⁸ It was thus natural that Ehrlich should exhibit an interest in arsenic, and he apparently tried atoxyl, a synthetic organic arsenic compound, in 1903 but rejected it because it did not exert a lethal action on the parasites in the test tube.³⁹ In 1902 Laveran and Mesnil had administered arsenious acid to experimental animals infected with trypanosomes, but they had been unable to effect a complete cure. After the publication of Ehrlich's results on trypan red in 1902, Laveran tried a combination of this dye with arsenious acid and found that in rats and mice it cured certain trypanosome infections that neither substance alone could treat successfully. These results were confirmed in Ehrlich's laboratory.⁴⁰

In 1905 Thomas and Breinl of the Liverpool School of Tropical Medicine reported that atoxyl, which Ehrlich had earlier abandoned on the basis of *in vitro* tests, could eliminate trypanosomes from the blood of infected animals.⁴¹ This discovery stimulated further interest in arsenicals on the part of Ehrlich and others, but it was soon found with respect to atoxyl that relapses commonly occur and that the large therapeutic doses required could damage the optic nerve and produce blindness in man.⁴² Even before this discovery of its effect on sight, however, Ehrlich was attempting to modify the structure of atoxyl to produce a less toxic and more potent trypanocidal drug.

Atoxyl had been synthesized in the 1860s by Béchamp, and was believed to be an anilide with little potential for modification to produce active derivatives. Ehrlich and Bertheim found that atoxyl was a chemically stable compound and possessed a free amine group which could be reacted with various substances to produce a host of related derivatives. The chem-

38. David Livingstone tried arsenic as early as 1858 as a remedy for a horse afflicted with *nagana*, a disease later found to be caused by a trypanosome. See David Livingstone, 'Arsenic as a remedy for the tsetse bite,' *Br. med. J.*, 1858, *i*, 360-361. Arsenic preparations were also tried by David Bruce in the 1890s in an effort to cure trypanosomal diseases. See John J. McKelvey, Jr., *Man against tsetse: struggle for Africa* (Ithaca, N.Y., 1973), pp. 27-28, 66, 84-85.

39. Ehrlich (n. 13), p. 283.

40. A. Laveran and F. Mesnil, 'Recherches sur le traitement et la prévention du Ngana,' *Annls. Inst. Pasteur*, 1902, *16*, 785-817; A. Laveran, 'Le trypanoth dans le traitement de quelques Trypanosomiasés,' *C. r. Séanc. Acad. Sci., Paris*, 1904, *39*, 19-22; Ehrlich, 'Chemotherapeutische' (n. 2), p. 85; letter from Ehrlich to A. Laveran, 13 February 1905, Ehrlich copybooks (n. 8), Ser. v, No. xvii, pp. 69-70.

41. H. W. Thomas and A. Breinl, *Report on trypanosomes, trypanosomiasés and sleeping sickness* (Liverpool, 1905); H. W. Thomas, 'Some experiments in the treatment of trypanosomiasés,' *Br. med. J.*, 1905, *i*, 1140-1141.

42. 'A danger of atoxyl,' *J. Am. med. Ass.*, 1907, *49*, 1149.

ists at the Georg-Speyer-Haus found that the toxicity of atoxyl could be increased or decreased by suitable modifications of the molecule.⁴³

As is well known, several hundred organic arsenic compounds were prepared and tested in Ehrlich's laboratory. This work was carefully directed by Ehrlich himself. Each morning he would provide the various researchers in his laboratory with written instructions for their day's work, and he expected these instructions to be obeyed exactly.⁴⁴ Sometimes such detailed supervision led to resentment on the part of experienced coworkers who felt that they should have more independence.⁴⁵ When he was in the process of searching for skilled chemists to work in his new institute for experimental chemotherapy, Ehrlich described to a colleague the difficulty of finding suitable candidates from his point of view. He noted: 'they must be on the one hand entirely skilled and independent scientific workers, and, on the other hand, also disposed to acquiesce in my ideas and develop them therapeutically.' Ehrlich admitted that the task of preparing the compounds that he desired might not always be of great interest from a purely chemical point of view.⁴⁶

In the course of the work on organic arsenic compounds it was found that only trivalent arsenic compounds killed trypanosomes *in vitro*, and Ehrlich postulated that the pentavalent atoxyl was converted to the trivalent state in the body. Particularly encouraging results were obtained with compounds of the arsenobenzene type R-As-As-R'. For example, compound number 418, arsenophenylglycine, yielded encouraging results in laboratory and clinical trials, but the search still continued in Ehrlich's institute for a better chemotherapeutic agent.⁴⁷

After the *Spirochaeta pallida* had been isolated as the causal agent of syphilis in 1905, several investigators tried arsenical drugs such as atoxyl in the treatment of syphilis and other spirochaetal diseases because of the

43. Paul Ehrlich and A. Bertheim, 'Über p-Aminophenylarsinsäure,' *Collected papers* (n. 2), III, 135-139 (*Ber. dt. chem. Ges.*, 1907); Ehrlich (n. 13), pp. 283-284; Ehrlich, 'Moderne Chemotherapie' (n. 11), pp. 141-142. See also letter from Paul Ehrlich to L. Darmstädter, 25 November 1905, Ehrlich copybooks (n. 8), Ser. v, No. XVIII, pp. 303-305, on the structure of atoxyl.

44. Marquardt, *Ehrlich* (n. 1), pp. 53, 63, 130, 133-134. Reid Hunt, working in Ehrlich's laboratory in 1902, noted that in his supervision of coworkers such as Mogenroth and Sacks, 'Ehrlich writes down what they are to do and will never hear a word of suggestion from any of them.' Letter from Reid Hunt to John Abel, 10 November 1902, Abel Papers, Johns Hopkins University. Hunt may have exaggerated somewhat, but Ehrlich did not want his coworkers to become too independent. I am grateful to the Johns Hopkins University Institute of the History of Medicine for permission to use the Abel papers.

45. See Marquardt, *Ehrlich* (n. 1), pp. 141-144, 154-156.

46. Letter from Paul Ehrlich to A. Wohl, 9 May 1905, Ehrlich copybooks (n. 8), Ser. v, No. XVII, pp. 100-105.

47. Ehrlich (n. 6), pp. 154-165; Ehrlich, 'Moderne Chemotherapie' (n. 11), pp. 141-149.

apparent similarity between trypanosomes and spirochaetes.⁴⁸ As in the case of trypanosomal infections, arsenic preparations had been used to some extent in the treatment of syphilis long before the cause of the disease was known.⁴⁹ Ehrlich's laboratory did not carry out experiments on syphilis-infected animals before 1909, but Ehrlich was interested in spirochaetes and did arrange for his friend Albert Neisser to test the most promising arsenicals on syphilis in monkeys and apes.⁵⁰

In 1909 Sahachiro Hata, who had carried out experimental studies on syphilis in rabbits at the Kitsano Institute of Infectious Diseases in Tokyo, came to work in Ehrlich's laboratory. Ehrlich set him to work testing the effects of numerous compounds on relapsing fever and on syphilis. When Hata tested compound number 606, he found it to be an effective anti-syphilitic agent. The compound had actually been synthesized in 1907, but the assistant who tested it at the time did not report any significant therapeutic activity. It is not clear why the effectiveness of 606 was missed at first, since the compound is, as was soon shown, useful in the treatment of certain trypanosomal diseases as well as syphilis.⁵¹

After extensive animal tests, limited supplies of 606 were distributed to selected specialists for clinical trials. In April 1910 Ehrlich was ready to announce the discovery of 606 at the Congress for Internal Medicine in Wiesbaden.⁵² The announcement was greeted with great enthusiasm, and the demand for the drug soon outgrew the ability of the Georg-Speyer-Haus chemists to produce it. Ehrlich then arranged with the Höchst Chemical Works to manufacture 606, which was patented under the trade-

48. See P. Uhlenhuth, E. Hoffmann, and K. Roscher, 'Untersuchungen über die Wirkung des Atoxyls auf die Syphilis,' *Dt. med. Wschr.*, 1907, 33, 873-876.

49. See John S. Haller, Jr., 'Therapeutic mule: the use of arsenic in the nineteenth century materia medica,' *Pharm. Hist.*, 1975, 17, 87-100; and Alfred Fournier, *Traitement de la syphilis* (Paris, 1893), pp. 100-104.

50. Ehrlich (n. 13), pp. 294-295. References to spirochaetes in Ehrlich's letters and notes in the Ehrlich copybooks (n. 8) before 1909 indicate his interest in these microorganisms and the diseases they cause. As an example of Neisser's studies, see Albert Neisser, 'Ueber die Verwendung des Arsacetins (Ehrlich) bei der Syphilisbehandlung,' *Dt. med. Wschr.*, 1908, 34, 1500-1504. See also Ehrlich's letter to Neisser, 12 April 1907, Ehrlich copybooks (n. 8), Ser. v, No. XXI, pp. 315-318.

51. Marquardt, *Ehrlich* (n. 1), pp. 163-175; Ehrlich (n. 13).

52. Paul Ehrlich, 'Allgemeines über Chemotherapie,' *Collected papers* (n. 2), III, 235-239 (*Verh. Kongr. inn. Med.*, 1910, 27, 226-234). The Ehrlich copybooks (n. 8) for 1909-10 provide information on the distribution of 606 for clinical trials. See also Marquardt, *Ehrlich* (n. 1), pp. 172-177. Some results of animal studies with 606, along with other compounds, were briefly noted in a lecture by Ehrlich on 1 December 1909, but 606 was not singled out for special attention. See Paul Ehrlich, 'Chemotherapie von Infektionskrankheit,' *Collected papers* (n. 2), III, 213-227, pp. 220-221, 226 (*Z. ärztl. Fortbild.*, 1909 6, 721-733).

name *Salvarsan*.⁵³ *Salvarsan* represented the first practical success for Ehrlich's concept of chemotherapy, and the only truly significant one during his lifetime.

Ehrlich, as we have seen, was very much interested in understanding the mechanism of action of drugs, for he believed that a rational therapeutics must be based on such an understanding. He emphasized that in a chemotherapeutic institute one must search for the scientific foundations of drug action rather than carry out a purely empirical search for new drugs.⁵⁴ The first duty of experimental pharmacology, according to Ehrlich, was to clarify not only the questions 'What?' and 'How?' but also 'Why?' Therefore, he had decided to investigate the cause of the action of arsenic.⁵⁵ His chemotherapeutic researches led him to reject his earlier conception of the view of drug action and to apply a modified form of the side-chain theory which he had used to explain immune reactions to the question of drug action. Particularly instrumental in this regard was the discovery in his laboratory of the phenomenon of drug resistance.

In the period from 1905 to 1907, experiments carried out by Franke, Röhl, and Browning in Ehrlich's laboratory demonstrated that a strain of trypanosomes that is susceptible to treatment with a particular drug, such as atoxyl, may, on continued exposure to that drug, develop a resistance to such treatment. In other words, a trypanosome strain may be produced that no longer responds to treatment with the drug. Resistance was found to be not limited to the compound used to develop it, but to extend also to other compounds within the same chemical class. For example, the atoxyl-resistant strain exhibited a significant degree of resistance towards other arsenical compounds, such as acetyl-atoxyl, and the trypan-red-resistant strain exhibited some resistance towards other azo dyes, such as trypan blue and trypan violet. The development of resistance towards one group of compounds (for example, the arsenicals), however, did not

53. Marquardt, *Ehrlich* (n. 1), pp. 176-180. For an example of the enthusiasm with which *Salvarsan* was greeted, see 'Doctors in Congress,' *London Times*, 12 August 1913 (a report on the International Congress of Medicine in London, where Ehrlich spoke). On the reception of *Salvarsan* in this country, see Patricia Spain Ward, 'The American reception of *Salvarsan*,' *J. Hist. Med.*, 1981, 36, 44-62. *Salvarsan* was not received enthusiastically by all. For discussions of opposition to the drug, which had potentially dangerous side effects, see Marquardt, *Ehrlich* (n. 1), pp. 234-238; and Harry Dowling, 'Comparisons and contrasts between the early arsphenamine and early antibiotic periods,' *Bull. Hist. Med.*, 1973, 47, 236-249, p. 245.

54. In referring to the tasks of a chemotherapeutic institute, Ehrlich wrote that one should not grab blindly like a bear in the soup bowl if one wanted a good piece. See his notes dated 7 September 1909, Ehrlich copybooks (n. 8), Ser. IV, No. v, pp. 19-20.

55. Ehrlich, 'Moderne Chemotherapie' (n. 11), p. 145.

increase resistance towards compounds of other classes (for example, azo dyes).⁵⁶

In order to explain the specificity of resistance, Ehrlich adopted the concept of *chemoreceptors* for drugs. In his Harben Lectures of 1907 in London, he revealed that he had come to believe that at least some drugs are bound to protoplasm by certain atom groupings ('side chains' or 'receptors'). The chemoreceptors for drugs are somewhat analogous to the toxin receptors, but are simpler in structure and less independent (that is, they cannot be separated from the cell to form antibodies). A given drug or poison, such as an arsenic compound, will only attack an organism, for example, a trypanosome, if that organism possesses chemoreceptors capable of combining with it. Like the *nutrireceptors* that are attacked by microbial toxins, however, chemoreceptors are ordinarily engaged with the normal substances of nutrition or metabolism, and hence are present in all cells. Hence, Ehrlich explained, any chemical drug is likely to have an affinity for the cells of the host organism as well as for the parasite. In order for a drug to be an effective chemotherapeutic agent, it must have a greater affinity for the chemoreceptors of the parasite cells than for those of the host cells, or its 'trypanotropic' force must be greater than its 'organotropic' force. In other words, one must be able to produce a curative effect with a dose that is not injurious to the host.

The studies on drug resistance, Ehrlich argued, supported the concept of chemoreceptors. The atoxyl-resistant strain, for example, was resistant to a number of arsenic compounds which otherwise possessed significant differences in their chemical characteristics. The arsenic acid radical, however, represented a common point of attack in this series. It was bound to the cell by chemoreceptors. The trypanosome cell possessed other chemoreceptors which represented the points of attack for other poisons.

The development of resistance could be readily explained by Ehrlich in terms of the receptor concept. The chemoreceptors of resistant trypanosome strains had somehow developed a reduced affinity for the drug, so that the distribution of the drug between the microorganisms and the host animal is shifted in the direction of the latter.⁵⁷ Ehrlich felt that the phe-

56. Ehrlich, 'Chemotherapeutische' (n. 2). See also Parascandola and Jasensky (n. 31), pp. 216-220, for a fuller discussion of the studies on drug resistance.

57. Paul Ehrlich, 'Experimental researches on specific therapy,' *Collected papers* (n. 2), III, 106-134, pp. 120-122, 132-133 (*The Harben Lectures for 1907 of the Royal Institute of Public Health* [London, 1908]). In his notes, Ehrlich wrote that chemical poisons are like wild birds that become captured and destroy the surroundings. See his notes of 28 March 1909, Ehrlich copybooks (n. 8), Ser. IV, No. IV, p. 380.

nomenon of drug resistance would play an important role in the development of 'therapeutic biology' and would help to bring order and light to the chaos of drug action.⁵⁸ Ehrlich's decision to apply the receptor concept to drugs was also influenced, as he himself admitted, by the development in 1905 of a similar theory of 'receptive substances' by John Newport Langley in England to explain the action of alkaloidal drugs such as nicotine and curare.⁵⁹

In his early discussions of the mode of action of arsenicals, Ehrlich emphasized the binding of the arsenic radical to a chemoreceptor in the cell. He even speculated about the chemical nature of the 'arsenoreceptor,' suggesting that it might be a hydroxyl or sulfhydryl group, a remarkably accurate prediction, because Carl Voegtlin later showed that the chemical grouping involved in reacting with arsenic is indeed a sulfhydryl group.⁶⁰ But Ehrlich soon developed a more complex explanation of drug action involving more than one receptor for a given drug.

As Ehrlich noted in 1909, if aromatic arsenic compounds were anchored to the cell exclusively through the trivalent arsenic atom bound on the phenyl residue and this anchorage was the determining factor in the action of this class of drugs, then one would expect that the simplest compounds (such as phenylarsenic acid and arsenobenzene) would be the best substances for treatment. But such was not the case. In fact, the introduction of substituents in the *para*-position of the benzene ring in phenylarsenic acid greatly influenced toxicity and therapeutic action. For example, the introduction of an amino group in this position promotes the action of the drug.⁶¹

In order to explain the fact that substitutions in the benzene ring, which do not affect the arsenic radical itself, modify the action of the drug, Ehrlich postulated that for complicated drugs other groupings in the molecule besides the arsenic residue are also involved in binding the drug to the cell. The addition, removal, or modification of such groups therefore affects the fixation of the compound to the cell and consequently its pharmacological action. The drug becomes successively fastened by its various groupings to the specific 'fangs' or 'snares' (*Fangen*), that is, the chemoreceptors, of the protoplasm. Ehrlich, in his usual graphic way, compared the process to the mounting of a butterfly which is fixed first by the torso and then succes-

58. See Ehrlich's notes of 13 May 1908. Ehrlich copybooks (n. 8), Ser. VI, No. IV, p. 422.

59. For a discussion of Langley's views, see Parascandola and Jasensky (n. 31).

60. See John Parascandola, 'Carl Voegtlin and the "arsenic receptor" in chemotherapy,' *J. Hist. Med.*, 1977, 32, 151-171.

61. Ehrlich (n. 6), pp. 164-165.

sively by the wings with pins. He noted, however, that one can frequently determine experimentally a grouping that brings about the primary anchoring, and that this grouping can be designated the *primary haptophore*. In the drug arsenophenylglycine (compound number 418), for example, Ehrlich felt that the acetic acid radical was the group that primarily anchored the drug to the cell.⁶²

Ehrlich was essentially applying the haptophore-toxophore concept, which he utilized in immunology, to the problem of drug action. Originally, before he adopted the receptor concept for drugs, Ehrlich had denied that drugs possessed haptophore groups. He had argued that the entire constitution of the drug was involved in its distribution rather than specific atom groupings. Even before he published his first account of his chemoreceptor theory, however, he had come to accept the idea that drugs possess a 'selective group,' which governs distribution, and a 'pharmacophore group,' which evokes the specific activity.⁶³ With the development of the drug-receptor theory, Ehrlich came explicitly to adopt the haptophore-toxophore terminology of his immunological theory (with the stipulation that there could be more than one haptophore group involved in binding a drug).

This fact is perhaps seen most clearly in Ehrlich's discussion of the mode of action of Salvarsan. Ehrlich expressed the point best at the International Congress of Medicine in 1913:

Now, if we are to look for specific medicaments, the first condition is that they must possess a certain definite group which is chemically allied to one of the chemoreceptors of the parasites. This is only one of the prerequisites necessary for the medicament to be effective, but generally it is not sufficient in itself. Hundreds of substances may fix themselves to a parasite but only a few are capable of bringing about destruction.

Thus, in the therapeutically suitable substance there must be present, in addition to the anchoring or haptophore group, which brings about the fixation, another group which brings about the destruction, and which, therefore, is characterized as the poisoning, or toxophore group. This concept exactly corresponds to the views which we have already held for years with respect to the toxins, in which we distinguish the presence of a haptophore group which causes the anchorage to the cell and also the formation of the antitoxins, and a toxophore group which brings about the injurious action on the cell. For the

62. Ehrlich, 'Infektionskrankheit' (n. 52), pp. 219-220; see also his notes of 6 February 1909, Ehrlich copybooks (n. 8), Ser. IV, No. IV, p. 324. Another metaphor that Ehrlich used was that one snares insects more easily with a bundle of lime twigs than with a single one. *Ibid.*, p. 479 (2 July 1909).

63. Ehrlich, 'Address' (n. 2), p. 57.

more complicated synthetic medicaments the assumption will have to be made that the haptophore group and the toxophore group are not directly connected with one another, but that they, as residues, are attached, like side-chains, to a chemical molecule. Thus, quite simply, the more complicated chemotherapeutic agents may be compared to a poison-arrow; the anchoring group of the medicament which anchors itself to the chemoreceptor of the parasite corresponds to the point of the arrow, the connecting link to the shaft, and the poison group to the arrow poison affixed to the shaft of the arrow. According to this scheme, in Salvarsan, dihydroxydiaminoarsenobenzene, the benzene nucleus would correspond to the shaft, the *o*-aminophenol group to the point, and the trivalent arsenic radicle to the poison. . . .

If, therefore, we poison a spirochaete with Salvarsan, at least two different chemical anchorages occur; first, the anchorage of the *o*-aminophenol group which primarily anchors the Salvarsan to the parasite. It is only in consequence of this anchorage that, second, the trivalent arsenic radicle is given the opportunity of entering into chemical combination with the arsenoceptor of the cell, and so of exerting its toxic action. The avidity of the arsenoceptor may, in itself, be so small that a reaction can take place only if favourable factors, which chemically must be regarded as steric facilitation, are operating. Examples of steric facilitations of this kind are frequently found in pure chemistry, e.g., in the chemistry of *ortho*-condensations. Thus the haptophore group of the arsenical primarily brings the arsenic into contact with the cell and secondarily provides an opportunity for its action.⁶⁴

Even before Ehrlich had applied the receptor concept to drugs, as we have seen, he had argued that the search for specific medicaments should be based on searching for substances that possessed a particular affinity for a certain organ and then using such substances as vehicles to carry therapeutically active groups to the organ involved. Now, however, this concept was expressed in terms of chemoreceptors. Ehrlich felt that the chemotherapeutist must aim to discover for every type of parasite the characteristic haptophore group with the aid of which one could force a specific therapeutic radical (such as arsenic) upon the parasite. One must, in other words, learn what chemoreceptors are possessed by specific parasites. The ideal situation would be to find a chemoreceptor that is present only in the parasite and not in the cells of the host. Ehrlich expressed his views about such an ideal substance:

I have explained above that the parasites possess a whole series of chemoceptors which differ specifically from each other. Now, if we were to succeed in dis-

64. Ehrlich (n. 3), pp. 507-508.

covering among these a receptor which was not represented in the organs of the host, we would have the possibility of constructing an ideal medicament by selecting a haptophore group which fits exclusively this particular receptor of the parasites. A medicament provided with such a haptophore group would be entirely innocuous, because it is not anchored by the organs; it would, however, strike the parasites with full force, and, in this sense, correspond to the immune-substances, the antibodies discovered by Behring, which, in the manner of magic bullets, seek out the enemy. Let us hope that it will also be possible, chemotherapeutically, to score bull's-eyes in this way. I do not consider this at all improbable, since it can be shown that, with certain diseases, e.g., spirillosis of fowls, from a fiftieth to a hundredth part of the *dosis tolerata* of Salvarsan entirely frees the animals from the parasites and brings about a cure. Such a dose truly represents a zero dose, as the fowl cannot be harmed by it to the slightest extent. But such favourable circumstances have been encountered only very rarely up to the present; we shall have to be satisfied if we can obtain good therapeutic results with a tenth, or even a fifth or sixth, part of the *dosis tolerata*.⁶⁵

As Ehrlich recognized, such ideal drugs would not be easy to find. We must often be satisfied to find substances that have a greater affinity for a particular chemoreceptor in a parasite than for the corresponding chemoreceptor in a human cell. A knowledge of the different chemoreceptors of a parasite, or what Ehrlich designated 'the therapeutic physiology of the parasite cell,' was for him 'a *sine qua non* for success in chemotherapy.' The larger the number of different chemoreceptors that could be demonstrated, the greater the possibility of successful chemotherapy.⁶⁶

Ehrlich's theoretical view of chemotherapy came to be based on the chemoreceptor concept. And the chemoreceptor concept in turn was based on Ehrlich's concept of the cell as a giant protoplasmic molecule with chemical side chains involved in various biological functions (what he termed *partial functions* of the cell). Acknowledging that this view of the cell had long been accepted by Pflüger and others, he claimed for himself the credit for removing this idea from the realm of the theoretical and making it accessible to experimentation. He felt that his analysis of the cell into partial functions would be a lasting contribution to biology.⁶⁷ In his Nobel Prize Address of 1909 he stated:

Even now the time has come to find a way into the finest chemistry of cell life, and to dissect the inclusive concept of the cell into a large number of single

65. *Ibid.*, p. 510.

66. *Ibid.*, p. 507.

67. Letter from Paul Ehrlich to J. G. Adami, 17 March 1909, Ehrlich copybooks (n. 8), Ser. v, No. XXV, pp. 401-402.

and specific 'partial functions.' Since, however, everything that happens in the cell is essentially chemical in nature, and since the configuration of chemical structure lies beyond the limit of visibility, we shall have to make a search for other methods of investigation. This line of thought has not only a general importance for a true understanding of the phenomena of life; it is also fundamental to a truly rational application of medicinal remedies.⁶⁸

In discussing the theoretical basis of his chemotherapy, mention should be made of two other concepts, or what Ehrlich called *therapeutic tactics*, which related to his understanding of drug action and guided his view of the practical application of chemotherapy. The first of these is his famous doctrine of *therapia sterilisans magna*, by which Ehrlich meant the elimination of all the parasites from the body by a single dose (or, at most, two doses). Ehrlich placed great emphasis on this goal, although he was not able actually to achieve it with Salvarsan in the treatment of syphilis. He seems to have been concerned to bring about the destruction of the parasites as quickly as possible and to avoid the possibility of having parasites that survived the first dose develop into a relapse strain that was resistant to the body's natural defense mechanisms and the drug.⁶⁹

The other therapeutic tactic is combination therapy, that is, the use of two or more drugs in combination to treat a particular infection. The idea of combination therapy with chemotherapeutic agents was not original to Ehrlich. I have already mentioned Laveran's use of this procedure. But Ehrlich placed great emphasis on this tactic. Combination therapy should be carried out, in Ehrlich's view, with therapeutic agents that attack different chemoreceptors in the parasite. There would be no advantage, for example, to combining trypan red with trypan blue, since both drugs have the same point of attack. Combining Salvarsan with parafuchsin, however, can be effective because these substances attack entirely different chemoreceptors. Ehrlich noted that 'once we have come to know most of the chemoreceptors of a particular parasite—and this will be an arduous task requiring much hard work and thinking—we shall have tremendous possibilities [for] attacking with various agents simultaneously.' Such a combination therapy had two important advantages.

First, one might be able in this way to increase the therapeutic effect without increasing the toxicity towards the host. The reason for such a possibility was that the receptors for parafuchsin were likely to be in organs

68. Paul Ehrlich, 'On partial functions of the cell: Nobel lecture,' *Collected papers* (n. 2), III, 183–194, p. 183 (Nobelstiftelsen, Stockholm, *Les prix Nobel en 1908* [Stockholm, 1909]).

69. Ehrlich (n. 3), pp. 512–514; Ehrlich (n. 13), p. 292.

other than those for Salvarsan; hence the two drugs would be localized in different cells in the human body and their toxic effects on these cells would not be additive. On the other hand, both drugs would accumulate in the unicellular parasite, and their effects on the parasite would be additive. Combination therapy in this way made possible a cure with smaller doses of each drug, thus reducing the chances of toxic side effects.

Secondly, resistance was less likely to arise if two drugs were used. If paraformaldehyde and Salvarsan were used in combination, for example, those organisms that were resistant to one drug would most likely be destroyed by the other, and a relapse strain would be less likely to develop. Even if a relapse did occur, the organism seemed to be less resistant to the drug involved when combination therapy had been employed.⁷⁰

The early successes in chemotherapy were concentrated in the area of diseases caused by protozoal-type microorganisms (for example, trypanosomes and spirochaetes), and significant progress was not made in the chemotherapeutic treatment of true bacterial infections until the development of the sulfa drugs in the 1930s. Sir Henry Dale suggested in his introduction to *The collected papers of Paul Ehrlich* that the publication by Ehrlich of the negative results of experiments with Bechhold on bacteria in 1906 seems to have discouraged him and others about the practicality of developing effective chemotherapeutic substances for bacterial infections.⁷¹ I do not believe, however, that this was the case. As Dale himself pointed out, Ehrlich became so involved with Salvarsan from 1909 until his death that he did not have time for research in other areas.⁷² But on several occasions Ehrlich expressed optimism concerning the successful application of chemotherapy to bacterial infections. He wrote to a colleague in 1909 that while he thought that the sterilization of bacteria within the body would be a very difficult task, he did not see it as impossible.⁷³ A few years later, he referred in a published lecture to some promising chemotherapeutic experiments that several investigators had carried out with bacteria and expressed the

70. Ehrlich (n. 3), pp. 514–515. The quotation is from p. 515. See also Ehrlich, 'Experimental' (n. 57), pp. 133–134.

71. Henry Dale, 'Introduction,' *Collected papers* (n. 2), III, 1–8, p. 5. Dale's claim has been repeated by M. P. Earles, 'Salvarsan and the concept of chemotherapy,' *Pharm. J.*, 1970, 204, 400–402, p. 401. The publication that Dale referred to is H. Bechhold and Paul Ehrlich, 'Beziehungen zwischen chemischer Konstitution and Desinfektionswirkung: ein Beitrag zum Studium der "inneren Antisepsis," ' *Collected papers* (n. 2), III, 64–80 (*Z. physiol. Chem.*, 1906, 47, 173–199).

72. Dale (n. 71), p. 6. For a discussion of the problems surrounding Salvarsan that so absorbed Ehrlich's time and energy, see Marquardt, *Ehrlich* (n. 1), pp. 188–206.

73. Letter from Ehrlich to L. Krehl, 3 February 1909, Ehrlich copybooks (n. 8), Ser. v, No. xxv, pp. 274–275.

view 'that in the next five years we shall see very extensive advances in this field.'⁷⁴

In the period from 1910 to 1930 a significant amount of research effort was devoted to attempts to find chemotherapeutic agents effective against bacteria, albeit without much success. The failure of such efforts certainly did lead in the 1920s to pessimism on the part of many scientists and physicians about the potential of bacterial chemotherapy.⁷⁵ This pessimism, however, owed more to the accumulation of negative findings over a period of years than it did to the publication of Ehrlich's disappointing results in 1906.

Ehrlich recognized that it was not necessary for a drug actually to kill the parasites in order for an infection to be eliminated from the body. There was evidence, he pointed out, that in some cases a drug prevented a microorganism from reproducing, and, by thus checking the infection, led to the eventual elimination of the parasite.⁷⁶ Sir Henry Dale has noted that since most of the antibacterial drugs discovered in recent decades act in this fashion (that is, they are bacteriostatic rather than bactericidal), it is unfortunate that Ehrlich did not find the time to follow up this concept. I do not think that Dale was justified in concluding that Ehrlich 'recognized this antireproductive effect as probably the most important factor in a practical chemotherapy.'⁷⁷ Neither Ehrlich's published writings nor the manuscript materials that I have examined devote a significant amount of attention to the antireproductive mechanism, and Ehrlich generally spoke in terms of a destruction of the parasites. The receptor theory could accommodate either mechanism, for the drug could be envisioned as either poisoning the microorganism or interfering with its ability to reproduce when it combined with the chemoreceptor. In either case the macroscopic result would be the same (assuming that the drug had been administered in time)—elimination of the parasite from the body of the host. While this question was thus not crucial to his general theory of drug action, it is certainly

74. Ehrlich (n. 3), pp. 516–517. The quotation is from p. 517.

75. For discussion of the growing pessimism, see Harry Dowling, *Fighting infection: conquests of the twentieth century* (Cambridge, Mass., 1977), pp. 105–107; and Iago Galdston, 'Some notes on the early history of chemotherapy,' *Bull. Hist. Med.*, 1940, 8, 806–818, pp. 816–817. For a contemporary view of the research efforts in bacterial chemotherapy, see Henry Dale, 'Chemotherapy,' *Physiol. Rev.*, 1923, 3, 359–393, pp. 363–367. Dale cited a significant number of studies, but concluded that the chemotherapy of bacterial infections 'cannot be said to have achieved, as yet, anything of practical importance' (p. 367).

76. Paul Ehrlich, 'Über die Neuesten Ergebnisse auf dem Gebiete der Trypanosomenforschung,' *Collected papers* (n. 2), III, 195–212, p. 209 (*Arch. Schiff's Tropenhyg.*, 1909, 13, Suppl. 6, 91–116).

77. Dale (n. 71), pp. 4–6. The quotation is from p. 6.

the kind of fundamental scientific problem that would have interested Ehrlich, and Dale may have been correct in speculating that Ehrlich would have investigated the subject further had he not been diverted in the last years of his life from more basic research to the practical problems surrounding Salvarsan.⁷⁸

Ehrlich's concept of chemotherapy and the practical success of Salvarsan stimulated a search for other effective chemotherapeutic agents as well as further research into the mechanism of drug action. The field of chemotherapy had been launched, and was to be guided by the general principles established by Ehrlich for many years to come. The theoretical basis of Ehrlich's chemotherapy, the side-chain theory, however, soon ran into difficulties. Even during his lifetime the view of the cell as a giant protoplasmic molecule with chemical side chains came under attack by such biochemists and physiologists as Frederick Gowland Hopkins and William Bayliss, and was eventually found untenable. Pharmacologists such as Walther Straub, Henry Dale, and Carl Voegtlin began to point out facts that were difficult to explain on the basis of the side-chain theory.⁷⁹ The basic concept of the drug receptor has, of course, survived to occupy a central place in theoretical pharmacology today, but in a form greatly modified from Ehrlich's conception of the chemoreceptor.

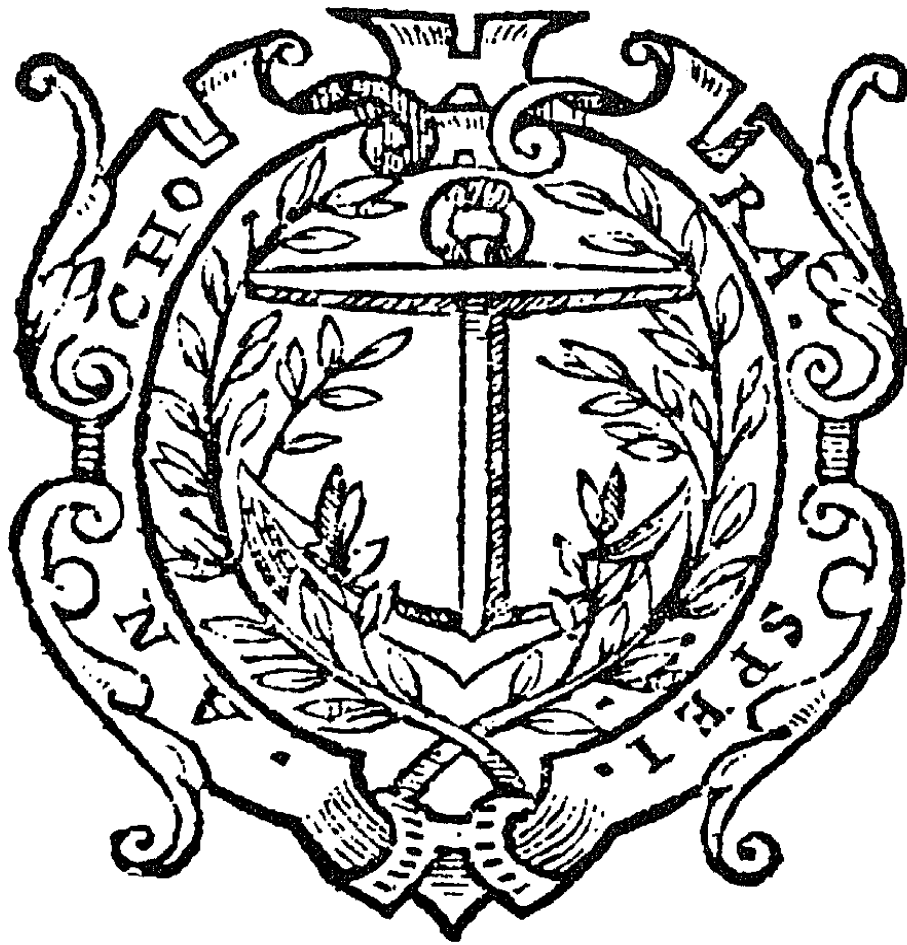
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78. *Ibid.*, p. 6.

79. For a discussion of some of the criticisms of Ehrlich's theory, see *Parascandola* (n. 60).

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