Styles in Scientific Explanation: Paul Ehrlich and Svante Arrhenius on Immunochemistry

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What are the great faults of Conversation? . . . I will tell you what I have found spoil more good talks than anything else:—long arguments on special points between people who differ on the fundamental principles upon which these points depend. No men can have satisfactory relations with each other until they have agreed on certain ultimata of belief not to be disturbed in ordinary conversation, and unless they have sense enough to trace the secondary questions depending upon these ultimate beliefs. . . . [A] code of finalities is a necessary condition of profitable talk between two persons.

Oliver Wendell Holmes, *The Autocrat of the Breakfast-Table*

SCIENTIFIC controversies often serve to expose the adversaries' tacit assumptions about the proper description of natural phenomena. Such assumptions impart individuality to a scientist's endeavors. Recently this question has been the subject of historical investigation: for example, Gerald Holton's *themata* in the development of physical theory, Gerd Buchdahl's posited *architectonic* dimension of scientific thought, and, in the context of biochemistry, Joseph Fruton's *styles* of scientific speculation.[1] Such schemes share the assertion that a researcher may be guided or informed by a personal set of underlying principles antecedent to and largely independent of empirical evidence. Some of

1. Gerald Holton, 'Presupposition in the construction of theories,' in Harry Woolf, ed., *Science as a cultural force* (Baltimore, 1964), pp. 77–108; idem, *Thematic origins of scientific thought: Kepler to Einstein* (Cambridge, Mass., 1973); idem, 'On the role of themata in scientific thought,' *Science*, 1975, *188*, 328–334; also see Robert K. Merton, 'Thematic analysis in science: notes on Holton's concept,' *Science*, 1975, *188*, 335–338; Gerd Buchdahl, 'History of science and criteria of choice,' *Minn. Stud. Phil. Sci.*, 1970, *5*, 204–230; Joseph S. Fruton, 'The emergence of biochemistry,' *Science*, 1976, *192*, 327–334. Pauline M. H. Mazumdar has employed 'styles of thought' in a similar way in her discussion of immunochemistry in 'Karl Landsteiner and the problem of species 1838–1968' (Ph.D. diss., Johns Hopkins University, 1976). For an alternative use of the term *style* see Erwin Chargaff, 'Triviality in science: a brief meditation on fashions,' *Perspect. Biol. Med.*, 1975, *19*, 324–333, p. 331.

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these principles or *themata* resurface one generation after another; they are long-lasting or persistent scientific assumptions.

Styles, in Fruton's sense of the word, are most pronounced in fields emerging from heterodox origins. A new field's workers and orientations may be drawn from several disciplines, and the contributing approaches may not be perceived as complementary. The turn of century debate between Mendelians and biometricians, which defined the intellectual space of classical genetics, is one case in point.[2] The various subfields of biochemistry are also rich with such examples,[3] and the biochemical controversy which set Svante Arrhenius against Paul Ehrlich in the first years of this century is an exemplary stylistic confrontation.

Arrhenius and Ehrlich debated the chemical description of the immune response. In the late 1880s researchers at the Pasteur Institute in Paris discovered that certain bacteria extrude soluble albuminous (protein) poisons, which were termed *toxins*. By 1891 Behring and Kitasato in Berlin reported that toxins from the diphtheria and tetanus bacilli elicit protective proteinlike substances in the blood serum of infected animals. The discovery of these specific antitoxins initiated both the study of humoral immunity and the clinical practice of serumtherapy. By century's end scientific consensus held the interaction of toxin (antigen) and antitoxin (antibody) to be an essentially chemical rather that purely physiological process. The perplexing and intricate mechanisms of that interaction, however, defied satisfactory explanation.[4]

Protagonists of the immunological debate generally followed two dominant chemical styles, the physicalist and the structuralist. The issue here is: does one interpret a given biochemical reaction *more fundamentally* by recourse to the molar physical properties of the reaction mix, or the reactants' molecular structures? The tension between these positions has been a general theme in the history of biochemistry. At a time when the distinction

2. This debate recently has been scrutinized from several perspectives: Robert de Marrais, 'The double-edged effect of Sir Francis Galton: a search for motives in the biometrician-Mendelian debate,' *J. Hist. Biol.*, 1974, *7*, 141–174; Lyndsay A. Farrall, 'Controversy and conflict in science: a case study—the English biometrical school and Mendel's laws,' *Soc. Stud. Sci.*, 1975, *5*, 269–301; Donald Mackenzie and Barry Barnes, 'Biometrician versus Mendelian: a controversy and its explanation,' *Köln. Z. Soziol. sozPsychol.*, 1975, *18*, 165–196; B. J. Norton, 'Biology and philosophy: the methodological foundations of biometry,' *J. Hist. Biol.*, 1975, *8*, 85–94.

3. I here refer to biochemistry in its broadest, though admittedly ahistorical, sense, that is, the study of biological phenomena with methods or concepts derived from chemistry. On the tension among biochemical styles see Fruton (n. 1).

4. A concise account of immunological theory and practice is W. D. Foster, *A history of medical bacteriology and immunology* (London, 1970). Also see Pauline M. H. Mazumdar, 'Immunity in 1890,' *J. Hist. Med.*, 1972, *27*, 312–324.

was drawn more sharply than it now could be, Arrhenius and Ehrlich insistently and eloquently championed these respective points of view.

Ehrlich's speculations matured amid the tradition of organic structural and synthetic chemistry that flowered in Germany during the second half of the nineteenth century. The salient points of that tradition were the supposedly high correlation between molecular structure and chemical affinity, and a concept of atomic bonding that may be called, albeit anachronistically, *covalent*. Ehrlich was adept at using these concepts heuristically in physiology and pathology as for instance in his side chain theory of immunity. Arrhenius, on the other hand, was a founding father of modern physical chemistry, which itself grew in the 1880s and '90s from mechanics and thermodynamics. The hallmarks of his biochemical research were an application of chemical kinetics and his theory of electrolytic dissociation to biological systems.

Although the versatility of these men tends to mask the underlying unity to the thought of each, fortunately they were unusually candid about what they took to be axiomatic in chemistry and biology. It can be seen that their adherence to one or the other chemical style resulted from the combined influences of education, professional circumstance, and idiosyncratic personal vision.[5] Their careers were remarkable for the persistence with which each probed the implications of a single unifying concept, arrived at while they were still students.

In the decades that straddled the year 1900, the differentiation between physical and chemical interactions had not yet blurred and the time was ripe for conflict among chemical schools.[6] The debate between Arrhenius and Ehrlich serves to clarify the pluralism inherent to the chemistry and biochemistry of that period. In a more general context, it may shed some

5. Cf. Thomas S. Kuhn, *The structure of scientific revolutions*, 2d ed. (Chicago, 1970); Gerald Holton, 'Finding favor with the angel of the Lord: notes toward the psychobiographical study of scientific genius,' in Yehuda Elkana, ed., *The interaction between science and philosophy* (Atlantic Highlands, N.J., 1974), pp. 349–387; Davis Robbins and Ron Johnston, 'The role of cognitive and occupational differentiation in scientific controversies,' *Soc. Stud. Sci.*, 1976, *6*, 349–368; Jonathan Harwood, 'The race-intelligence controversy: a sociological approach,' *Soc. Stud. Sci.*, 1977, *7*, 1–30; Thomas L. Hankins, 'Triplets and triads: Sir William Rowan Hamilton on the metaphysics of mathematics,' *Isis*, 1977, *68*, 175–193.

6. 'Colloid chemistry' was the third 'school' which contributed to immunochemical speculation. The three positions are summarized in Pauline M. H. Mazumdar, 'The antigen-antibody reaction and the physics and chemistry of life,' *Bull. Hist. Med.*, 1974, *48*, 1–21. An introduction to the literature is provided by Jules Bordet, 'Sur le mode d'action des antitoxines sur les toxines,' *Annls Inst. Pasteur*, 1902, *17*, 161–186. On colloid chemistry more generally, see Wolfgang Ostwald, 'Zur Frage nach der kolloidchemischen Analyse des Specifizätsprobleme,' *Biochem. Z.*, 1913, *48*, 225–229; S. G. Mokrushin, 'Thomas Graham and the definition of colloids,' *Nature*, 1962, *195*, 861; Joseph S. Fruton, *Molecules and life: historical essays on the interplay of chemistry and biology* (New York, 1972), pp. 131–148.

light on the issue of how a scientist constructs his or her ontology. Finally, Arrhenius and Ehrlich frequently fell back upon their experience in, respectively, physics and the biomedical sciences. Since disciplinary gaps in approaches here persist, though perhaps narrowed, the debate addresses issues of continuing concern in biochemistry and biophysics.

An Evolution of Two Styles

Paul Ehrlich (1854–1915), a native of the environs of Breslau (now Wroclaw, Poland), studied medicine at the University of Breslau. During a second semester spent at the newly founded German university in Strasbourg, he began to experiment with aniline staining of tissues and also 'experienced an intense interest' in chemistry, especially organic chemistry.[7] He later remarked: 'I . . . believe that my real natural endowment lies in the domain of Chemistry; and mine is, indeed, . . . a kind of visual, three-dimensional [eine chemisch-plastische] Chemistry. The benzene-rings and structural formulae really disport themselves in space before my mind's eye. . . . I might say, indeed, that my chemical imagination was very strongly developed. . . .'[8] The choice of imagery and the reference to benzene strongly suggest a parallel to August Kekulé, discoverer of the benzene ring and a nonpareil structural chemist.[9] Their highly developed visual and stereognostic imagination provides a clue to the particular form of

7. Biographical information was culled from: Richard Koch, 'Paul Ehrlich,' in Günther Bugge, ed., *Das Buch der Grossen Chemiker*, 2 vols. (Berlin, 1929–30), II, 421–442; English trans. in Eduard Farber, ed., *Great chemists* (New York and London, 1961), pp. 1039–1063; Martha Marquardt, *Paul Ehrlich* (New York, 1951); *Dictionary of scientific biography*, s.v. 'Ehrlich, Paul.' The essays comprising *Paul Ehrlich: Eine Darstellung seines wissenschaftlichen Wirkens* (Jena, 1914) are invaluable for a consideration of Ehrlich's career. Fielding H. Garrison's 'Ehrlich's specific therapeutics in relation to scientific method,' *Pop. Sci. Mon.*, 1911, *78*, 209–222, is a classic account of Ehrlich as scientist. The quoted phrase is taken from an autobiographical sketch submitted to Christian Herter in 1901 and reproduced in Paul Ehrlich, *The collected papers of Paul Ehrlich*, ed. P. Himmelweit et al., 4 vols. (London and New York, 1956–60), I, 9.

8. Ehrlich, *Collected papers* (n. 7).

9. Kekulé was an architecture student at the University of Geissen when he was attracted to organic chemistry by Justus Liebig's lectures. 'This circumstance,' he later claimed, 'and the direction which my earlier architectural studies gave my intellect—*an irresistable urge to visualize everything*—these seem to be the reasons why the chemical ideas which were in the air twenty-five years ago found suitable soil inside my head': quoted by Herbert C. Brown, 'Foundations of the structural theory,' *J. chem. Educ.*, 1959, *36*, 104–110. Kekulé's famous account of discovery while riding a London omnibus one summer evening in 1854 reinforces the comparison with Ehrlich. 'I sank into a revery [*Träumerei*],' he recalled. 'The atoms were gamboling [*gaukelten*] before my eyes. I had always seen these diminutive entities in motion, but up to that time I could never discern the kind of motion': quoted in Richard Anschütz, *August Kekulé*, 2 vols. (Berlin, 1929), I, 50; also cited by J. R. Partington, *A history of chemistry*, 4 vols. (London, 1964), IV, 537.

scientific creativity at which they excelled, the construction of a molecular architecture.[10]

In Ehrlich's case, he endeavored throughout his scientific career to elucidate biological specificity in terms of chemical affinities and configurations. In the introduction to his collected *Studies in immunity* he professed: 'I have been more and more forcibly impressed with the idea that in a study of the fundamental biological phenomena, the significance of morphological structure is far less than the significance of the chemistry involved.'[11] Likewise, he opened his Nobel Lecture of 1908 by stating his belief that the investigation of 'the configuration of chemical structure' will come to supersede anatomy as the major thrust of biology and medicine.[12] The tools Ehrlich most often used to this purpose were color changes induced in cells and tissues by the application of particular dyes. These studies prepared the way for his subsequent work in immunology.

As a student in Julius Cohnheim's pathological institute at Breslau Ehrlich immersed himself in aniline dye histology.[13] A colleague later recalled, 'Do you remember Ehrlich as a student in Breslau? We laughed at him because he was always running around among us with blue, yellow, red and green fingers. . . .'[14] This work culminated in his M.D. dissertation, 'Contributions to the theory and practice of histological staining.' The thesis lay unread until 1919 when Ehrlich's student Leonor Michaelis unearthed it from the University of Leipzig archives. Michaelis immediately realized that it contained the nascent speculations that were to reach fruition in the side chain theory.[15]

Among Ehrlich's other pertinent preimmunological investigations should

10. The ability to think in terms of three-dimensional structures and their relations, as one might expect, also has been a hallmark of great anatomists. For instance, Carl Ludwig once praised his student Franklin Paine Mall as a born anatomist possessed of 'ein hochentwickelter Raumsinn': letter from Ludwig to Mall, 24 October 1893, reproduced in Florence Rena Sabin, *Franklin Paine Mall: the story of a mind* (Baltimore, 1934) pp. 329–330. Sabin further reported that Mall often said that he would have liked to study architecture (pp. 57–58).

11. Paul Ehrlich et al., *Studies in immunity*, 2d ed., trans. Charles Bolduan (New York, 1910), p. vi.

12. Paul Ehrlich, 'Ueber Partialfunktionen der Zelle,' in Nobelstiftelsen, Stockholm, *Les prix Nobel en 1908* (Stockholm, 1909); in *Collected papers* (n. 7), III, 171–182; English trans. pp. 183–194, p. 183.

13. Ehrlich's first publication, 'Beiträge zur Kenntniss der Anilinfärbungen und ihrer Verwendung in der mikroskopischen Technik,' *Arch. mikrosk. Anat. EntwMech.*, 1877, *13*, 263–277; in *Collected papers* (n. 7), I, 19–28, revealed the discovery of a new type of stainable granular cells which he named *mast* cells.

14. Quoted in Carl Julius Salomonsen, 'Reminiscences of the summer semester, 1877, at Breslau,' trans. C. Lilian Temkin, *Bull. Hist. Med.*, 1950, *24*, 333–351, p. 336.

15. Paul Ehrlich, 'Beiträge zur Theorie und Praxis der histologischen Färbung' (M.D. diss., University of Leipzig, 1878); in *Collected papers* (n. 7), I, 29–64; English trans., pp. 65–98. Leonor Michaelis, 'Zur Erinnerung an Paul Ehrlich: Seine wiedergefundene Doktor-Dissertation,' *Naturwissenschaften*, 1919, *7*, 165–168.

be mentioned his *Habilitationsschrift* of 1885, *The oxygen requirement of the organism.*[16] Again, he employed dyes, introducing the powerful technique of vital staining to refine and amend physiologist Eduard Pflüger's theory of cellular respiration.[17] A notion championed by Pflüger and popular among late nineteenth-century investigators trained in physiology or medicine rather than chemistry was that the cell's protoplasm is a giant labile molecule of 'living protein.'[18] Despite meager evidence, workers repeatedly used it to account for cellular respiration and nutrition. Ehrlich readily accepted this concept of the giant cellular molecule, 'which bears the same relation to the ordinary chemical molecule,' he said, 'as the sun does to the smallest meteorite.'[19] In its support he cited the precedent of Kekulé's chemistry of aromatic compounds: there the benzene ring is relatively stable, and reactivity depends on the type and distribution of 'side chains.' In similar fashion, he felt, one could now comprehend the cell's vitality: '[L]iving protoplasm [is] a [chemical] nucleus of special structure which determines the specific, characteristic function of the cell, and to this nucleus there attach themselves as side chains molecules [Atome] and molecular complexes which are of subsidiary importance for the specific cellular activity, but not so for life as a whole.'[20]

This, then, was the conceptual and methodological apparatus with which Ehrlich, in the aftermath of the discovery of antitoxins, approached humoral immunity. As Sir Henry Dale later pointed out, it is unlikely that Ehrlich would have regarded immunological research as a diversion from the line of his earlier activities. He would be ready to assume the chemical nature of antitoxin action and the necessity for the use of chemical methods and ideas.[21]

The immunological work began with a series of brilliant studies on two

16. Paul Ehrlich, *Das Sauerstoff-Bedürfnis des Organismus: Eine farbenanalytische Studie* (Berlin, 1885); in *Collected papers* (n. 7), I, 364–432; English trans., pp. 433–496. As later noted, the 'idea of measuring chemical energies by means of reversible processes was far ahead of his time': Hugo Bauer, 'Paul Ehrlich's influence on chemistry and biochemistry,' *Bull. N.Y. Acad. Sci.*, 1954, *59*, 150–167, p. 151.

17. For example, Eduard Pflüger, 'Beiträge zur Lehre von der Respiration. I. Ueber die physiologische Verbrennung in den lebendigen Organismen,' *Pflügers Arch ges. Physiol.*, 1875, *10*, 251–367. See Charles A. Culotta, 'A history of respiratory theory: Lavoisier to Paul Bert, 1777–1880' (Ph.D. diss., University of Wisconsin, 1968), ch. 4; Fruton, *Molecules and life* (n. 6), pp. 277–299.

18. On the reactive constituents of the cellular molecule see Joseph S. Fruton, 'Energy-rich proteins, 1870–1910,' in Conference on the historical development of bioenergetics, Boston, 1975, *Proceedings of the conference . . .* (Boston, 1975), pp. 17–35.

19. Ehrlich, *Das Sauerstoff-Bedürfnis* (n. 16), English trans., p. 436.

20. *Ibid.* This translation is taken from Fruton, *Molecules and life* (n. 6), p. 296. Both the terms *Kern* (chemical nucleus) and *Seitenketten* (side chains) were in common usage among nineteenth-century organic chemists.

21. Sir Henry Dale, 'Introduction,' in Ehrlich, *Collected papers* (n. 7), II, 2.

highly toxic proteins of castor beans (ricin) and jequirity seeds (abrin).[22] As contrasted to the then rather ill-defined bacterial toxins, these doses could be accurately determined by weight. Ricin held out the further advantage of yielding a visible quantifiable effect in the test tube, namely, the agglutination of red blood cells. Equipped with this first manageable in vitro system, he determined that toxin and antitoxin do indeed combine according to the law of multiple proportions and, hence, can be described by straightforward stoichiometric equations.

Robert Koch soon welcomed Ehrlich onto the staff of his new Institute for Infectious Diseases. There, collaborating with Emil Behring, Ehrlich produced a concentrated potent diphtheria antiserum suitable for human use.[23] In 1896 Friedrich Althoff, Prussian Minister for Ecclesiastical, Educational and Medical Affairs, secured for Ehrlich the directorship of an Institute for Serum Research and Serum Testing located in a converted farm building in the Berlin suburb of Steglitz. He was charged with developing an accurate assay for the antitoxic activity of therapeutic sera, a problem that had perplexed previous researchers.

From serum therapy's outset it had become clear that prepared standardized diphtheria antisera either spontaneously or on standing attenuated below usable potency.[24] Since toxins and antitoxins could be neither purified nor weighed by any available method, Ehrlich tackled the problem by devising a purely empirical standard. Arbitrary standards were familiar in physical science, as for instance the bar which represents the internationally recognized unit of one meter, but they were unexploited in biology. Ehrlich's standard, the 'unit of immunity' (Immunitätseinheit), was represented by a stable reference serum stored under special conditions. He now approached the toxicity problem.

Animals infected with diphtheria toxin produce antibody to it in their blood; the blood serum may then be extracted for use as therapeutic antitoxin. It was well known that by varying the dosage of injected toxin one could produce antitoxin of a given desired potency. Ehrlich discovered

22. Paul Ehrlich, 'Experimentelle Untersuchungen über Immunität: I. Über Ricin,' *Dt. med. Wschr.*, 1891, *17*, 976–979; in *Collected papers* (n. 7), II, 21–26. Paul Ehrlich, 'Experimentelle Untersuchungen über Immunität: II. Über Abrin,' *Dt. med. Wschr.*, 1891, *17*, 1218–1219; in *Collected papers* (n. 7), II, 27–30.

23. Within two years, after Behring independently contracted with the Hoechst pharmaceutical firm for commercial diphtheria antitoxin production, the relationship soured. See Marquardt, *Ehrlich* (n. 7), pp. 32–40.

24. Thorwald Madsen, *Experimentelle Undersøgelser over Difterigiften* [*Experimental researches on the toxin of diphtheria*] (Copenhagen, 1896); 'Report of the Lancet Special Commission on the relative strengths of diphtheria antitoxic serums,' *Lancet*, 1896, ii, 182–195.

that when he administered diphtheria toxin in increasing doses—in this case to produce a potency of one I.E. /cc of serum—he could nearly always distinguish two operational threshold values: when the toxin is completely neutralized by antitoxin (termed L_0); and after *additional* toxin is added to the neutralized mixture sufficient to kill a 250-gram guinea pig within four days of intraperitoneal injection (termed L_+ or Limes Tod). This least additional quantity of toxin he designated the minimal lethal dose (MLD). Thus, $L_+ - L_0 = \text{MLD}$, provided that the toxin is a pure chemical substance.

The caveat was that in practice the number of lethal doses (MLD) contained in a single test dose (L_+) could vary by several orders of magnitude. Ehrlich's conclusion was that a toxin's neutralizing capacity is *distinct* from its toxicity. He conjectured that toxin molecules are transformed into non-toxic decomposition products, toxoids, which nevertheless retain their specific affinity for antibody. The results were presented in a classic paper in 1897, 'The assay of the activity of diphtheria-curative serum and its theoretical basis,' an article as unfortunate for its lack of coherent development as for its cumbersome prose.[25]

Ehrlich proposed, in line with his previous studies, that toxin molecules combine with certain metabolic side chains (nutriceptors) of host cell protoplasm, thereby inhibiting normal cell functions. If the toxin does not kill the cell these nutriceptors must be regenerated. His cousin and teacher, Carl Weigert, had previously postulated a general biological principle: a damaged cell or tissue will hyperregenerate a missing part.[26] Ehrlich leapt to the conclusion that in this manner the excess of newly regenerated nutriceptors 'will become too much for the cell itself and will be discharged into the blood, like an excretion, as unwanted ballast. *According to this view, the antibodies represent side chains of the cell protoplasm which have been produced in excess and therefore thrust off.*'[27] This mechanism accounts for the exquisite specificity of an antibody for the toxin eliciting it. Ehrlich further suggested that antitoxin and toxin may interact akin to the 'lock and key'

25. Paul Ehrlich, 'Die Wertbemessung des Diphtherieheilserums und deren theoretische Grundlagen,' *Klin. Jb.*, 1897, *6*, 299–326; in *Collected papers* (n. 7), II, 86–106; English trans., pp. 107–125. Also see Claude E. Dolman, 'Paul Ehrlich and William Bulloch: a correspondence and friendship (1896–1914),' *Clio Med.*, 1968, *3*, 65–84.

26. Carl Weigert, 'Neue Fragestellungen in der pathologischen Anatomie,' *Verh. Ges. dt. Naturf. Ärzte*, 1896, *1*, 121–139. On Ehrlich and Weigert's relationship see Bruno Heymann, 'Zur Geschichte der Seitenkettentheorie Paul Ehrlichs,' *Klin. Wschr.*, 1928, *7*, 1257–1260; also Paul Ehrlich, 'Weigerts Verdienste um die histologische Wissenschaft,' in R. Rieder, ed., *Carl Weigert* (Berlin, 1906); in *Collected papers* (n. 7), III, 595–597.

27. Ehrlich (n. 25), p. 115. Original emphasis.

fitting of enzyme to substrate which had been proposed by the organic chemist Emil Fischer.[28]

Over the next several years Ehrlich and his co-workers engaged in extensive programmatic studies of immunity to toxins, bacteria, and foreign red blood cells.[29] In 1900 in the Croonian Lecture before the Royal Society of London, Ehrlich presented a fuller and more lucid exposition of the side chain theory.[30] He explained that a toxin molecule anchors to a cell nutri-

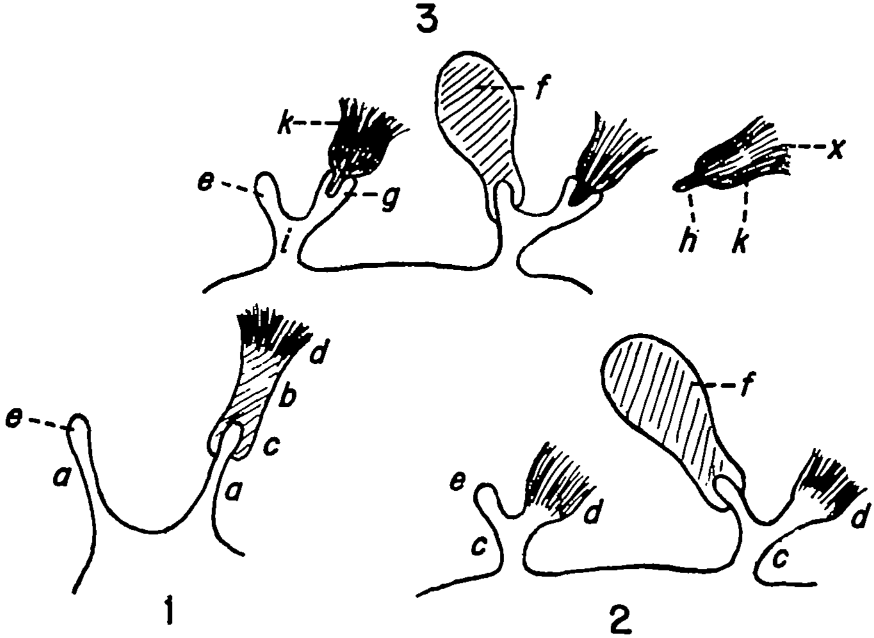


Fig. 1. Representation of Ehrlich's receptors. 1. First-order receptor (*a*): *e* haptophore complex, *b* attached toxin molecule with its haptophore (*c*) and toxophore (*d*) groups. 2. Second-order receptor (*c*) with haptophore (*e*) and zymophore (*d*) groups. Attached food molecule (*f*). 3. Third-order receptor (*i*): *e* haptophore group, *g* complementophile group, *k* complement with haptophore (*h*) and 'zymotoxic' (*z*) groups. Attached food molecule (*f*). Redrawn from Ludwig Aschoff, *Ehrlich's Seitenkettentheorie und ihrer Anwendung au; die kunstlichen Immunisierungsprozesse* (Jena, 1905).

28. For example, Emil Fischer, 'Einfluss der Configuration auf die Wirkung der Enzyme,' *Ber. chem. Ges. Frankfurt*, 1894, *27*, 2985–2993, 3479–3483; 1895, *28*, 1429–1438.

29. Red blood cells provided a convenient system; their destruction by antitoxin (hemolysis) could be observed in vitro and quantified. For a history of the Steglitz institute see W. Dönitz, 'Bericht über die Thätigkeit des jönoglichen Instituts für Serumforschung und Serumprüfung zu Steglitz, Juni 1896 – September 1899,' *Klin. Jb.*, 1899, *7*, 1–26.

30. Paul Ehrlich, 'On immunity with special reference to cell life,' *Proc. roy. Soc. Lond.*, 1900, *66*, 424–448; in *Collected papers* (n. 7), II, 178–195.

ceptor by means of a haptophore (grabbing) group; the toxin's other toxophore (poisonous) group thereby is brought into proximity with the cell. In effect, a toxin acts as a poisonous foodstuff and, consequently, the study of immunity becomes a department of general physiology. Ehrlich chose to argue his position from the standpoint of physiological economy. It would be superfluous, he reasoned, to assume that the organism contains the array of molecular groups destined to unite with the range of bacterial, animal, and plant toxins, which themselves serve no physiological function. Rather, it is by pure chance that they possess the capacity to anchor to any particular toxin.[31]

Ehrlich defined three classes of cell receptors that could account for the constellation of immunological phenomena. Cell receptors of the first order were the usual type encountered in toxin-antitoxin neutralization. Second-order receptors produced macroscopic end products, that is, the agglutination of red blood cells and precipitation of bacteria. Second-order receptors contained a haptophore group and an ergophore or zymophore —a recognition of the analogy to enzyme action—which facilitated the clumping of the foreign material. Third-order receptors, amboceptors, induced hemolysis, the destruction of red cells. These receptors were endowed with two haptophores; one would combine with toxin and the other, complementophile-one with complement, a serum factor required for hemolysis. The amboceptor, when shed into the circulation as humoral antibody, bridged toxin and complement to form a lytic complex.

'Complex organic compounds,' Ehrlich later reiterated, 'have repeatedly been shown to contain groups which confer definite properties upon the whole molecule.'[32] His entire experience in dye chemistry, toxicology, and immunology bore on this point. Herein lay the basic conviction behind Ehrlich's work: if a molecule exhibited two definable properties it *must* contain two spatially distinct active sites. Certainly, then, he was justified to refer to his work as 'structural chemistry' and 'synthetic organic chemistry' for wherever possible his concepts, techniques, and analogies were drawn from the corpus of organic chemical thought that had emerged among the generation of Justus Liebig's students and reached new heights

31. *Ibid.*, pp. 183–184.

32. Paul Ehrlich, 'Herter lectures,' *Boston med. surg. J.*, 1904, *150*, 443–450; 'Lecture I. The mutua relations between toxin and antitoxin,' pp. 443–445; in *Collected papers* (n. 7), II, 410–414, p. 410. A similar 'schematic example' using benzaldehyde appears in Paul Ehrlich and J. Morgenroth, 'Ueber Haemolysine,' *Berl. klin. Wschr.*, 1901, *38*, 251–257, 569–574, 598–604; in *Collected papers* (n. 7), II, 234–245; English trans. pp. 246–255.

of sophistication at the end of the nineteenth century in the elegant investigations of Emil Fischer.

Ehrlich's emphasis on pictorial chemical schemes manifested itself in two ways. First, one observes his penchant for using color to demonstrate cellular mechanisms. The hours he spent while a physician at Berlin's Charité Hospital in the 1880s surrounded by his bottles of dyes led one student wag to quip, 'Ehrlich färbt am langsten' ('Ehrlich dyes all the time') as a twist on the German proverb 'Ehrlich währt am langsten' (loosely: honesty is the best policy).[33] And in later years Ehrlich is reported to have expressed a wistful desire that he had become a dye chemist.[34] During a rather maudlin mood amidst his personal crisis of 1887 he wrote to his brother-in-law: 'When I felt so miserable and forsaken . . . , I often stood before the cupboard in which my collection of dyes was stored and said to myself: "These here are my friends which will not desert me. . . ." '[35] The other side of his visual imagination displayed itself as an avowed attraction to molecular configuration and three-dimensionality. It is not unreasonable to see the fondness for color and the acute sense of spatial relations as two facets of an eidetic facility that contributed substantially to his science.[36]

Svante Arrhenius (1859–1927) pursued a different course in chemical research. Arrhenius, who was raised in Uppsala, Sweden, displayed a precocious aptitude for arithmetic, and at an unusually early age began to study mathematics, physics, and chemistry.[37] After advancing through his doctoral disputation at the University of Uppsala, he moved to the University of Stockholm to pursue his experimental work. Much like Ehrlich, Arrhenius was an independent student. His professor, the physicist Erik Edlund, Arrhenius later wrote, 'did not encourage me very much to continue with chemical ideas, because he did not understand them very well. He was a pure physicist, but I had some ideas of my own.'[38]

33. Marquardt, *Ehrlich* (n. 7), p. 23.

34. Bauer (n. 16).

35. Quoted in Marquardt, *Ehrlich* (n. 7), p. 28. The original source is Felix Pinkus, 'Paul Ehrlich geboren 14 März 1854, gestorben 20 August 1915,' *Medsche Klin.*, 1915, *11*, 985, 1116–1117, 1143–1145.

36. Ehrlich's friend Christian Herter put it succinctly: 'Throughout his career Ehrlich has sought to use his knowledge of histology and chemistry to gain light on the processes of life. The clarity of his visual perceptions and the tenacity of his visual memories have enabled him to cultivate a sort of chemistry peculiarly suited to this aim.' From Christian A. Herter, *Imagination and idealism in the medical sciences* (Chicago, 1910), p. 29.

37. Biographical sources are: Sir James Walker, 'Arrhenius memorial lecture,' *J. chem. Soc.*, 1928, *3*, 1380–1401; Wilhelm Palmaer, 'Arrhenius,' in Bugge, ed., *Grossen Chemiker* (n. 7), pp. 443–462, English trans. in Farber, ed., *Great chemists* (n. 7), pp. 1093–1109; Ernst H. Reisenfeld, *Svante Arrhenius* (Leipzig, 1931); *Dictionary of scientific biography*, s.v. 'Arrhenius, Svante August.'

38. S. Arrhenius, 'Electrolytic dissociation,' *J. Am. chem. Soc.*, 1912, *34*, 353–364, p. 357.

By merging Edlund's electrical interests with his own in chemistry, in due course Arrhenius confronted the problem of conductivity in solutions. Although several investigators at midcentury, notably Johann W. Hittorf, Rudolf Clausius, and Rudolf Kohlrausch, had studied the distribution and migration of ions in electrolytes, that is, in solutions conducting electrical current, the ubiquity of electrolytic (ionic) dissociation remained unrecognized. Arrhenius's remarkable doctoral dissertation written in 1884, 'Researches on the galvanic conductibility of electrolytes,' reported that the process of solution is itself sufficient to free ions, and the degree of dissociation depends primarily on the nature of the solute and the degree of its dilution.[39] From the outset he treated the ionic moieties as the seats of chemical affinity. As was the case for Ehrlich, a lifetime's speculations were presented in embryo at this doctoral stage. Exhibiting the confidence that he would bring later to his biological studies, Arrhenius concluded his thesis with the claim that chemical knowledge is for the most part based on the reactions of electrolytes, 'which seem to play the same role in chemistry that gas does in the mechanical theory of heat.' Besides, he wrote, reactions in general seem to manifest a considerable analogy to those of electrolytes, 'so that perhaps one could in the future enlarge the theory given for electrolytes until it becomes, with some modifications, applicable to all substances.'[40] Chemical affinity, in this view, is purely a matter of electrodynamic forces. The corollary claim is that the theory of electrolytic dissociation provides the basis for a comprehensive chemistry.

Arrhenius's examiners were initially unimpressed, but the timely intercession of the distinguished physical chemist Wilhelm Ostwald saved him from obscurity. Over the next decade, first in the great physics laboratories of Europe and then as professor of physics at the University of Stockholm, the theory of electrolytic dissociation took definitive shape.[41] After victory for 'the wild army of Ionians,' as his supporters were dubbed, the energetic Swede looked for new fields to conquer. He also wished to demonstrate

39. S. Arrhenius, *Recherches sur la conductibilité galvanique des électrolytes* (Stockholm, 1884). Also see his Nobel lecture, 'Development of the theory of electrolytic dissociation,' in Nobelstiftelsen, Stockholm, *Nobel lectures . . . chemistry, 1901–1921* (Amsterdam, 1966), pp. 45–58.

40. Arrhenius, *Recherches* (n. 39), pt. 2, p. 89. In some measure, his expectations have been fulfilled. Johannes Nicolaus Brønsted and Thomas Martin Lowry in 1923 independently extended the theory of acids and bases to encompass proton-acceptor and proton-donor species. Later Gilbert Newton Lewis further generalized the concept of acidity.

41. On the dissertation's lack of impact see the comments of Per T. Cleve, chairman of the Nobel Committee for Chemistry and Arrhenius's chemistry professor at Uppsala, in Nobelstiftelsen, Stockholm, *Les prix Nobel en 1903* (Stockholm, 1906), pp. 48–49; Arrhenius's response, pp. 50–52. Also see Arrhenius, 'Aus der Sturm- und Drangzeit der Lösungstheorien,' *Chemisch weekblad*, 1913, *10*, 584–599.

that the natural sciences could be reconstituted along new lines, and he sought to fulfill the impetuous claims of his doctoral dissertation of a decade and a half earlier. In time, Arrhenius would try to interpret biology, geology, and astrophysics as specialized regions of ionic interactions.[42] In a retrospect in 1912 he wrote: 'Solutions play the most important role in the world: therefore the alchemists said that there is nothing which acts chemically but solutions. Solutions fill the oceans, solutions are running in our veins and solutions form the chief part of all organisms: life is bound to solutions, as well as chemical reactivity.'[43] The phenomena of humoral immunity offered Arrhenius his first chance to extend his ideas to biology.

The Immunochemical Controversy: 'Biology vs. Physical Chemistry'

In 1899 Ehrlich assumed the directorship of a new Royal Prussian Institute for Experimental Therapy at Frankfort on the Main. Among the researchers from several nations who assembled there was a young Danish bacteriologist, Thorvald Madsen, who had studied at Copenhagen with Ehrlich's Breslau compatriot C. J. Salomonsen. Madsen spent several months at the institute occupied with tetanolysin, the paralyzing exotoxin of the tetanus bacillus.[44]

In 1901 Madsen journeyed to Stockholm for several months' study under Arrhenius. Evidently, he expected that physicochemical techniques might facilitate an understanding of toxin-antitoxin neutralization. In all likelihood Madsen first aroused Arrhenius's interest in the field of *immunochemistry*, a term Arrhenius later coined.[45] Later in 1901 Arrhenius went to the new Danish State Serum Institute in Copenhagen to resume a collaboration with Madsen, and they set to tackling the problems associated with the test-tube reactions of tetanolysin with antilysin (antibody) and with red cells. Madsen handled the experimental work and pathology while Arrhenius assisted in arranging the protocols and interpreted the chemical

42. Arrhenius's wide-ranging studies included a *Lehrbuch der kosmischen Physik* (Leipzig, 1903) and numerous papers on meteorology, vulcanology, astrophysics, etc. His final publication bore the speculative title of 'Die thermophilen Bakterien und der Strahlungsdruck der Sonne,' *Z. phys. Chem.*, 1927, *130*, 516–519.

43. Arrhenius (n. 38), pp. 363–364. That year Arrhenius also dedicated to Jacques Loeb the publication of his Silliman Lectures at Yale University, *Theories of solutions* (New Haven, 1912), 'In admiration of his application of physical chemistry to biology.'

44. T. Madsen, 'Ueber Tetanolysin,' *Z. Hyg. InfektKrankh.*, 1899, *32*, 214–238. For biographical data see *Biographisches Lexikon der hervorragenden Aerzte der letzten fünfzig Jahre*, s.v. 'Madsen, Thorwald.'

45. S. Arrhenius, *Immunochemistry: the application of the principles of physical chemistry to the study of the biological antibodies* (New York, 1907); idem, 'Immunochemie,' *Ergebn. Physiol.*, 1908, *7*, 480–551.

data.[46] The following summer Arrhenius and Ehrlich were both on hand for the opening ceremonies of the Danish State Serum Institute. (Madsen was installed as director shortly afterwards.) After meeting, Ehrlich invited Arrhenius to the institute at Frankfort. Arrhenius accepted and spent part of 1903 and the beginning of 1904 there.[47]

Ehrlich was then engrossed in studying the role of complement in hemolysis. Jules Bordet, complement's discoverer, had claimed that an antibody (amboceptor) acts as a sensitizer of red blood cells when they are attacked by complement. Ehrlich believed that antibody and complement actually bind stereospecifically to yield a compound hemolysin.[48] Although Arrhenius's point of view did not coincide with his own, Ehrlich anticipated that the issue could be resolved by quantitative methods, and suggested that the necessary determinations be made. Arrhenius soon found that the degree of hemolysis increased with increase of either antibody or complement, but that sufficient amounts of both must be present; excess of one and deficiency of the other would not induce complete hemolysis. The data indicated that neither antibody nor complement act, as Bordet suspected, as a catalyst or sensitizer. However, Arrhenius upheld Bordet's assertion of the unitary nature of complement, and he took the opportunity to refine his own interpretation of hemolysis as analogous to a reaction between a weak acid and a weak base.[49]

46. S. Arrhenius and T. Madsen, 'Physical chemistry applied to toxins and antitoxins,' in Carl Jul. Salomonsen, ed., *Festskrift ved Indvielsen af Statens Serum Institute* (Copenhagen, 1902). Also see S. Arrhenius and T. Madsen, 'The molecular weight of diphtheria toxin,' *ibid.*; C. J. Salomonsen, 'The rise and growth of the State Serum Institute,' *ibid.* The first of these articles was reprinted as 'Anwendung der physikalischen Chemie auf das Studium der Toxine und Antitoxine,' *Z. phys. Chem.*, 1903, *44*, 7–62.

47. Snelders, in his DSB article on Arrhenius (n. 37), incorrectly set the time as summer 1902. A report of Arrhenius's recollection of his sojourn in Ehrlich's institute is presented in Anders Lundgren, 'Arrhenius om van't Hoff och Ehrlich. Två brev från Ernst Reisenfeld' [Arrhenius on van't Hoff and Ehrlich. Two letters from Ernst Reisenfeld], *Lychnos*, 1975–1976, pp. 85–100. The article is in Swedish, the text of the letters in the original German. Reisenfeld was Arrhenius's student and later his biographer (see n. 37).

48. For example, Paul Ehrlich and Hans Sachs, 'Ueber den Mechanismus der Amboceptorenwirkung,' *Berl. klin. Wschr.*, 1902, *39*, 492–496; in *Collected papers* (n. 7), II, 334–341.

49. For Arrhenius's account of his research in Frankfort see *Immunochemistry* (n. 45), p. vi, and his *Quantitative laws in biological chemistry* (London, 1915), p. 129. 'Complement' is actually a series of serum factors (zymogens, proteolytic enzymes, and their split products) that participates in many immunological and other pathophysiological processes. Biochemist Michael Heidelberger once properly observed: 'Complement activity was a very strange property [at that time] that led to all kinds of arguments. One can find almost any statement in the literature about complement and one can find the exact opposite and very often both are true under different experimental conditions.' From M. Heidelberger, *Lectures in immunochemistry* (New York, 1956), p. 3. For an early assessment by one of the discoverers of complement (alexine) see Hans Buchner, 'Sind die Alexine einfache oder complexe Körper?' *Berl. klin. Wschr.*, 1901, *38*, 854–857.

A controversy took shape in 1903 when Ehrlich responded in print to the criticisms leveled by Arrhenius and Madsen.[50] The actual debate was relatively brief. Arrhenius remained active in the field for a decade and published approximately two dozen papers and a book, *Immunochemistry*. He and Madsen continued their collaboration both in Copenhagen and at the Nobel Institute for Physical Chemistry in Stockholm. Ehrlich, on the other hand, by 1906 had largely eschewed immunology in order to devote his time to chemotherapy and the search for the *therapia sterilans magna*. The defense of his side chain theory was taken up by its votaries.[51]

While their debate was most intense, Ehrlich spoke of weathering his 'northern storm.'[52] Yet neither he nor Arrhenius allowed matters to degenerate into the polemics so common to academic disputation of the period. 'Svante,' as he was known among the usually decorous scientific *Geheimraten*, possessed a reputation for conviviality and wit. Ehrlich admired him, reserving his contempt for his more scurrilous personal attackers, such as the serologist Max von Gruber.[53] Arrhenius, in turn, respected Ehrlich's ability, though he disparaged Ehrlich's autocratic and bureaucratic style of research.

The substance of their disagreement typified the competitive, often antagonistic, relations between the communities of organic and physical chemists. Arrhenius's studies of the stoichiometry and kinetics of antigen-antibody reactions convinced him that the familiar sorts of chemical equilibria applied. After all, these reactions were reversible and obeyed Guldberg and Waage's law of mass action, the reactant concentrations were proportional to reaction velocity, and temperature influences were within recognizable limits. Consequently, he plotted numerous neutralization and toxicity curves for his data similar to the curves obtained for highly dissociated electrolytes. These interrelated issues of reversibility and the nature of binding were the critical points of contention.

50. Their critique had been set forth to a wider audience by the republication of their work in the *Zeitschrift für physikalische Chemie* (n. 46).

51. For example, Max Neisser, 'Kritische Bemerkungen zur Arrheniusschen Agglutinin-Verteilungsformel,' *Zentbl. Bakt. ParasitKde.*, 1904, *36* (*Abt. I*), 671–676; Hans Sachs, 'Ueber den Standpunkt Bordets in der Toxinfrage,' *Zentbl. Bakt. ParasitKde.*, *37* (*Abt. I*), 398–400.

52. Paul Ehrlich, 'Herter lectures,' *Boston med. surg. J.*, 1904, *150*, 443–450; 'Lecture II. Physical chemistry *v.* biology in the doctrines of immunity,' pp. 445–448; in *Collected papers* (n. 7), II, 414–418, p. 418.

53. See, for example, Max von Gruber, 'Neue Früchte der Ehrlichschen Toxinlehre,' *Wien klin. Wschr.*, 1903, *16*, 791–793; idem, 'Toxin und Antitoxin. Eine Replik auf Herrn Ehrlichs Entgegnung,' *Münch. med. Wschr.*, 1903, *50*, 25–28; idem, 'Bemerkungen zu Ehrlichs "Entgegnung auf Grubers Replik,"' *Münch. med. Wschr.*, 1903, *50*, 2297. On this controversy see Richard Wagner, *Clemens von Pirquet: his life and work* (Baltimore, 1968), pp. 30–43; and Mazumdar, 'Landsteiner' (n. 1), pp. 154–183, 222–267.

Arthur Croft Hill's 1898 discovery that an enzyme of degradation (maltase) could, under the proper conditions, catalyze synthesis lent credence to Arrhenius's intuition that biochemical processes take place in dynamic solutions.[54] Ehrlich, to the contrary, believed that a real *chemical* bond was formed between antigen (toxin) and antibody in the serum. For him the union was *not* the loose ionic sort, and the neutralization was essentially irreversible. Arrhenius replied to this point disdainfully. The objections of 'the old [*sic*] Ehrlich theory' that the processes are not reversible because the compound of toxin and antibody changes with time so that it becomes less dissociable he thought merely foolish. '[O]n the same ground,' he complained, 'we might oppose the use of reversible processes for the calculations of thermodynamics, because ideal reversible processes are in general not realized in nature.'[55]

In his doctoral dissertation, Ehrlich had first emphasized the importance of an insoluble lake for dye action. Thereafter, he continually stressed the necessity of connectedness for chemical reactivity. A favorite saying of his later years was: 'If *corpora non agunt nisi liquida* is a law that holds for chemistry, then *corpora non agunt nisi fixita* has a like authority on chemotherapy.'[56] His assertion held with equal force immunologically, because he maintained that the molecules must chemically interact by joining in lock and key fashion. As if in counterpoint, Arrhenius once claimed that 'The alchemists' experience was summed up in the two sentences: "Corpora non agunt nisi soluta" [substances do not interact unless they are dissolved] and "Salia non agunt nisi dissoluta, nec agunt si dissoluta nimis" [salts do not react unless they are dissolved, neither do they act if too much diluted].'[57]

Ehrlich pointed out that frequently in chemistry an intermediate product is unstable and the reaction is at that step reversible. If a stable product is then formed, usually by hydrolysis, the overall reaction is irreversible.[58] He believed the union of antigen and antibody to be of this kind, and he pressed the matter in his Nobel Lecture where he discussed a variety of toxin-antitoxin decompositions. Treatment with hydrochloric acid, he

54. A. C. Hill, 'Reversible zymohydrolyses,' *J. chem. Soc.*, 1898, *73* (*Pt. 2*), 634–658; idem, 'Reversibility of enzyme or ferment action,' *J. chem. Soc.*, 1903, *83*, 578–598.

55. Arrhenius, *Quantitative laws* (n. 49), p. 124.

56. Paul Ehrlich, 'Concluding remarks,' in P. Ehrlich and S. Hata, *The experimental chemotherapy of spirilloses*, trans. A. Newbold (New York, 1911), pp. 117–156; in *Collected papers* (n. 7), III, 251–281; English trans., pp. 282–309, p. 282.

57. Svante Arrhenius, 'The theory of electrolytic dissociation,' *J. chem. Soc.*, 1914, *105*, 1414–1426, p. 1415. *Dissoluta*, to be more precise, should be translated as 'dissolved' in both instances.

58. Commentary (p. 674) on Arrhenius's paper, 'Die Serumtherapie vom physikalisch-chemischen Gesichtspunkte,' *Z. Elektrochem.*, 1904, *10*, 661–664.

claimed, would resolve neutralized complexes of diphtheria or snake venom into their original components, 'just as in pure chemistry stable compositions such as the glucosides, when acted on by acids, are resolved into their two components, sugar and the constituent aromatic group.'[59]

Although these men's differences were representative of the broader divisions within chemistry, Arrhenius's position was not held unanimously by physical chemists. In May 1904, Arrhenius delivered a paper on serum therapy before the German Bunsen-Gesellschaft for Practical Physical Chemistry.[60] Jacobus van't Hoff chaired the session and he and the chemists Walther Nernst, Wilhelm Ostwald, Georg Bredig, and Paul Ehrlich contributed to the ensuing discussion. The growing influence of colloidal interpretations was evident from several comments, including Nernst's. But Nernst also lashed out at Arrhenius's work, claiming that his results were 'a mere [*blosse*] interpolation formula' unsupported by experiment. 'If one assumes Arrhenius's idea of equilibrium,' he charged, 'I cannot understand how to explain immunization. The bonding is supposed to be loose. But, in general, it is assumed that the free toxin is anchored by the tissues.' Nernst, Arrhenius's putative scientific ally, concluded that his friend's entire scheme was improbable since 'the conception of a reversible process collides with the facts of the study of immunization.'[61]

Nonetheless, Arrhenius held adamantly to the full applicability of the laws of chemical equilibria. In pressing the issue he revealed his scientific presuppositions. In the preface to *Immunochemistry* he stated that, despite the demonstration of the applicability of the laws of equilibrium,

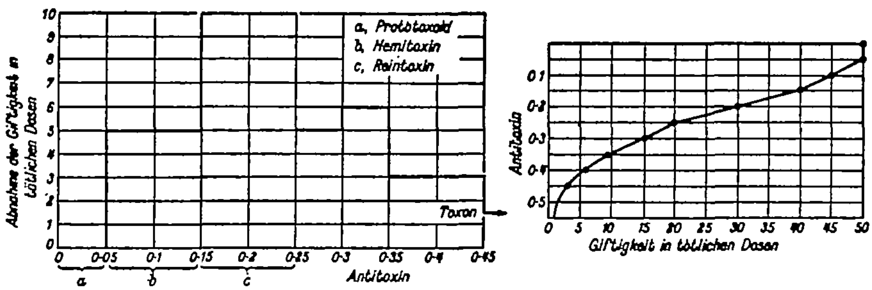
> one of the strange incidents with which the history of science is replete occurred. In an explanation of the investigated phenomena, especially regarding diphtheria toxin, Madsen and I, in accordance with the usual rule in the exact sciences, tried to employ as few hypotheses as possible, and in this we followed the example of Bordet. We tried to show that the phenomena observed might be explained on the supposition that diphtheria toxin is a simple substance which slowly decomposes into an innocuous material that still neutralizes antitoxin. In this explanation Ehrlich had previously assumed the presence in the diphtheria poison of a large number of poisonous substances of different strength. Now Ehrlich did not wish to yield this explanation, which he regards as the principal

59. Ehrlich (n. 12).
60. Arrhenius (n. 58).
61. *Ibid.*; Nernst commentary, pp. 676–677. Nernst's arguments were reiterated in his 'Ueber die Anwendbarkeit der Gesetze des chemischen Gleichgewichts auf Gemische von Toxin und Antitoxin,' *Z. Elektrochem.*, 1904, *10*, 377–380. According to Partington the incident precipitated Nernst's and Arrhenius's estrangement; see Partington, *History of chemistry* (n. 9), IV, 674.

point in his doctrine; and therefore he and his numerous pupils raised a number of objections to the treatment of this branch of science in accordance with the modern theories of chemistry.[62]

By 'the modern theories of chemistry' Arrhenius really meant physico-chemical theory. Evidently his standards for a chemical theory included two criteria of simplicity: 'as few hypotheses as possible' and simple substances.[63]

On the first point, a telling criticism of Ehrlich's scheme was that he postulated numerous modified toxins. Arrhenius justifiably complained that 'nearly every new phenomenon led Ehrlich and his school to invoke the presence of a new substance.'[64] Thermal or chemical stimuli could, in Ehrlich's view, modify either haptophore or toxophore group to facilitate or inhibit function. In his 'partial neutralization' experiments, for example, Ehrlich graphed the decrease of toxic doses neutralized by successive aliquots of antitoxin. He concluded that this diminution followed a stepwise pattern and, hence, that there exist discrete zones of neutralization. In order



Giftspektrum nach EHRLICH

Absättigungskurve nach ARRHENIUS und MADSEN

Fig. 2. Ehrlich's poison spectrum compared with Arrhenius's and Madsen's neutralization curve. From Paul Ehrlich and Hans Sachs, *Ueber die Beziehungen zwischen Toxin und Antitoxin und die Wege ihrer Erforschung* (Leipzig, 1905).

62. Arrhenius, *Immunochemistry* (n. 45), pp. vi–vii. Privately, Arrhenius referred to the 'Wust von greichischer Nomenklatur' of Ehrlich's explanations; Lundgren (n. 47), p. 96. Cf. Hans Buchner's attack on Ehrlich using grounds of 'economy of thought' in Buchner, 'Zur Kenntniss der Alexine, sowie der specifisch-bactericiden und specifisch-haemolytischen Wirkung,' *Münch. med. Wschr.*, 1900, *47*, 277–283. Mazumdar, 'Landsteiner' (n. 1), provided an excellent discussion of the immunology of Buchner and Gruber (classmates and fellow students of Carl von Nägeli.)

63. Simplicity is, to say the least, an exceedingly complex matter. See: Stuart Silvers, 'Discussion: some comments on Quine's analysis of simplicity,' *Philosophy Sci.*, 1964, *31*, 59–61; David F. Lardner, 'The axiom of simplicity in the development of chemistry,' *J. chem. Educ.*, 1966, *43*, 490–491; W. V. Quine and J. S. Ullian, *The web of belief* (New York, 1970), ch. 5; Nelson Goodman, *Problems and projects* (Indianapolis and New York, 1972), ch. 7.

64. Arrhenius, *Immunochemistry* (n. 45), p. 28.

to display these zones he developed a histogram, the 'poison spectrum.' There is a graphic distinction, in every sense of the word, between these poison spectra and Arrhenius's asymptotic neutralization curves.

The curve represents the reaction between two compounds of weak affinity, as in the case of highly dissociated electrolytes. For the most common instance: [Free Toxin] × [Free Antitoxin] = k[Toxin-Antitoxin Complex]^2. This representation certainly is the less clumsy and is more familiar to a present-day reader. Moreover, for more complicated cases, Ehrlich's veritable zoo of prototoxoids, syntoxoids, epitoxoids, toxins, etc., tangled his theory in Gordian complexity. Remarkably, Ehrlich firmly believed that the comparison was favorable. The two graphic methods 'are equally correct,' he wrote, although the poison spectrum 'has certain advantages, for it brings out more clearly *any deviations from the regular curve.*'[65] In this curious sort of reverse calculus he took tangents along a rate of change (neutralization) so as to construct a series of rectangles representing the different constituents of a toxin mixture. If the neutralization curve was a straight line, the poison spectrum would have one tangent, one rectangle and hence one constituent toxin. For the curves actually observed, he represented the directions of separate regions of a curve as ordinates, resulting in a complicated spectrum of many zones.

The basic issue was that Ehrlich had no sympathy for a practice since taken up wholesale from physical science, namely, the fitting of data to curves. The curve held little intrinsic interest for him because he considered it an artifact that masked the more fundamental series of discontinuities. 'The tedious work which these authors [Arrhenius and Madsen] have undertaken,' he asserted, 'may perhaps satisfy a mathematician; to the biologist, however, it can only represent useless and dangerous playing with figures.'[66] The irony was that Ehrlich had introduced quantitation into immunology. But he simply could not accept that toxin-antitoxin neutralization was the monomolecular reaction implicit in Arrhenius's continuous curve.

During his early experience with diphtheria standardization, Ehrlich observed that the first aliquot of antitoxin generally neutralized a greater portion of toxin than the second aliquot, this in turn greater than the third, and so forth. This so-called 'Ehrlich's phenomenon' was readily explain-

65. Paul Ehrlich and Hans Sachs, *Ueber die Beziehungen zwischen Toxin und Antitoxin und die Wege ihrer Erforschung* (Leipzig, 1905); in *Collected papers* (n. 7), II, 423–431. This translation appears in Ehrlich et al., *Studies* (n. 11), p. 552. Emphasis is mine.

66. *Ibid.*, pp. 555–556. Also see Ehrlich, 'Ueber die Giftcomponenten des Diphtherie-Toxins,' *Berl. klin. Wschr.*, 1903, *40*, 793–797, 825–829, 848–851; in *Collected papers* (n. 7), II, 347–367, p. 367.

able if one postulated that a toxin really consists of many partial toxins (toxoids) in which the species of greatest affinity is neutralized first and the weakest last. Such a family of discrete substances was the familiar stock of the organic chemist. The saltatory spectrum, despite its baroque profusion of components, in the light of Ehrlich's training might seem appropriate.

Arrhenius believed that the observed variations in neutralization were accounted for sufficiently by changes in acidity, concentration, and other parameters over the course of the reaction. He made the devastating criticism that if one applied Ehrlich's pluralistic scheme to the neutralization of ammonia by boric acid (which follows a similar curve), one must then assume that there exists a series of partial ammonias.[67] Ehrlich emphatically denied that he had 'violated the principle of choosing the simplest explanation. Such explanations received always my first consideration,' he maintained, 'and, as in the case of diphtheria-toxin, gave place to more complex ones only when the experimental results made this necessary.'[68]

Arrhenius's second stated criterion of simplicity, his invocation of simple substances, placed him on shakier ground. Carrying this principle to its extreme he was, in fact, prepared to conjecture that 'even the so-called simple poisons' are actually composed of two associated substances, the one toxic, the other possessing the affinity for antibody.[69] Ehrlich's organic chemical training predisposed him to the opposite view; a toxin is not two simple molecules, but rather one complex molecule with two spatially distinct functional sites. This chasm between the two positions was unbridgeable. Each man argued from his own considerable chemical expertise derived from different chemical realms.

The 'picturesque complexities' of Ehrlich's theory, as Sir Henry Dale felicitously termed them, could not fit with Arrhenius's two criteria for scientific parsimony. As an additional source of conflict, Arrhenius was complacent about his lack of training in organic chemistry or biology, believing that his education in the borderland between physics and chemistry was adequate for the study of biological problems. Ehrlich, who asserted that physical chemistry was a necessary but insufficient basis upon which to build biology, went so far as to entitle his second Herter Lecture at the Johns Hopkins University, 'Physical chemistry *v.* biology in the doctrines of immunity.' Elsewhere he stated, 'The natural aim of physical chemistry must always be to produce as few factors as possible for purposes

67. For example, Arrhenius, *Immunochemistry* (n. 45), p. 177.
68. Ehrlich (n. 66), p. 184.
69. Arrhenius, *Immunochemistry* (n. 45), p. 184.

of calculation whereas biological analysis always seeks to pay due regard to the wonderful multiplicity of organic matter.' Ehrlich conceded that a combination of the two methods is desirable: the biologist needed to restrict his assumptions to the fewest possible so as to yield to 'the economy of the mathematical view' while the physical chemist was obligated to pay due heed to experimentally validated minimal multiplicity.[70] Though these statements are self-serving, the problem Ehrlich posed is nevertheless valid.[71]

For Arrhenius, however, the issue was not so much that biologically minded investigators appreciated, or even overappreciated, biological complexity as that they were deficient in scientific exactitude. He took upon himself the task of spreading the gospel of exact science:

> ... I am convinced [he wrote] that biological chemistry cannot develop into a real science without the aid of the exact methods offered by physical chemistry. The aversion shown by biochemists, who have in most cases a medical education, to exact methods is very easily understood. They are not acquainted with such elementary notions as 'experimental errors,' 'probable errors,' and so forth, which are necessary for drawing valid conclusions from experiments. The physical chemists have found that the biochemical theories, which are still accepted in medical circles, are founded on an absolutely unreliable basis and must be replaced by other notions agreeing with the fundamental laws of general chemistry.[72]

In summary, Ehrlich and Arrhenius were at a loss to translate their respective ideas into the common language of a shared conceptual framework. What Ehrlich saw as a modicum of necessary premises Arrhenius regarded as gratuitous theoretical baggage. Their inability to arrive at an understanding may illustrate a more general phenomenon in the development of scientific disciplines. More recent workers, for instance, who have sought to integrate physical and biological methods and concepts have faced very similar problems. A biochemist of recent vintage, John Northrop, described the tensions between biologists and chemists in terms nearly identical to those of Arrhenius. For instance, Northrop wrote that 'chemists (and physicists) have great respect for the Reverend Occam's razor and endeavor to limit their assumptions to the minimal number essential for an explanation, in accordance with the principle of the conservation of hypotheses; whereas some biologists have no respect for the

70. Ehrlich (n. 66). The translation appears in Ehrlich et al., *Studies* (n. 11), pp. 512–513.

71. Few philosophers have dealt with the issue. On biological complexity, see Ernst Mayr, 'Discussion: footnotes on the philosophy of biology,' *Philosophy Sci.*, 1969, *36*, 197–202.

72. Arrhenius, *Quantitative laws* (n. 49), p. vi.

Reverend's weapon and fearlessly bolster an ailing (and unnecessary) assumption by another similar one.'[73] Ethologist Konrad Lorenz has chosen to be a spokesman for a different view and has written that biologists 'do not . . . forget the immensely complicated structures in which [physicochemical] processes perform their wonderfully organized integrating interactions. We do not push them aside as undesirable "intervening variables." '[74] The Ehrlichism is not fortuitous; today's ethology, like the physiology and pathology of Ehrlich's day, is becoming at once more quantitative and statistical, and is moving from a largely natural historical approach to the consideration of more general laws of nature.

The Resolution

The source of theoretical confusion between Arrhenius and Ehrlich arose from the putative differentiation between physical and chemical phenomena and the related question of the nature of the chemical bond. In 1905 few investigators heeded Karl Landsteiner's perceptive judgment that 'because of the lack of a sharp dividing line between so-called physical and chemical processes, the discussion as to whether [immunological] reactions are one or the other is meaningless.'[75]

Change was fostered by the important studies of Gilbert N. Lewis, an American who had studied under Ostwald and Nernst. Twenty years after the 1896 discovery of the electron, Lewis proposed that the chemical bond consists of an electron pair shared by two atoms.[76] In his 1923 book, *Valence and the structure of atoms and molecules*, Lewis recounted a history of the tension between the 'electrochemical or dualistic theory' and structural organic chemical concepts.

Must we conclude [he asked] that there are two distinct types of chemical union, one a completely polar and the other a completely non-polar type, and must we assume that a substance which appears to have intermediate properties, and to be slightly polarized electrically, is merely a mixture of polar and non-polar molecules? Or can we find some means of ascribing all the most valid types of chemi-

73. John H. Northrop, 'Biochemists, biologists, and William of Occam,' *A. Rev. Biochem.*, 1961, *30*, 1–10, p. 1. Not surprisingly, Northrop praises Arrhenius's biochemical research (p. 2).

74. Konrad Z. Lorenz, 'The fashionable fallacy of dispensing with description,' *Naturwissenschaften*, 1973, *60*, 1–9, pp. 3–4. Lorenz does, however, 'confess to a slight feeling of inferiority when I realize that I have never in my life published a paper with a graph in it' (p. 4).

75. Karl Landsteiner and M. Reich, 'Ueber die Verbindung der Immunokörper,' *Zentbl. Bakt. ParasitKde.*, 1905, *39*, 83–93, quoted in Mazumdar (n. 6), p. 18.

76. G. N. Lewis, 'The atom and the molecule,' *J. Am. chem. Soc.*, 1916, *38*, 762–785.

cal union to one and the same fundamental cause, differing only in the nature and degree of its manifestation?[77]

His answers set the stage for the modern conception of ionic and covalent bonding.[78]

Linus Pauling, in his influential text *The nature of the chemical bond*, offered this deliberately and almost painfully vague definition: 'We shall say that there is a chemical bond between two atoms or groups of atoms in case that the forces acting between them are such as to lead to the formation of an aggregate with sufficient stability to make it convenient for the chemist to consider it as an independent molecular species.'[79] Four decades after the onset of the Arrhenius-Ehrlich controversy, Pauling's evasiveness was the price to be paid for inclusivity. In all subsequent formulations covalent, ionic, and metallic interactions have been regarded as specialized instances of the broader class of electronic phenomena.

In retrospect, then, one may pinpoint the limitations of the schemes of Ehrlich and Arrhenius, neither of which was intrinsically incorrect. Undeniably, Ehrlich was right when he asserted that antigen and antibody bind stereospecifically. His incorrect assumption was that a firm chemical, that is, covalent, linkage existed. And although Arrhenius's analogy to weak acids and weak bases was misleading in many of its implications, the interactions are, in good measure, electrostatic.

Neither scientist questioned the other's data. On the contrary, they utilized each other's experimental results, and their conflict rather was one of interpretation. There was, however, one exception. Arrhenius claimed

77. G. N. Lewis, *Valence and the structure of atoms and molecules* (New York, 1923), p. 22. Also see Robert E. Kohler, Jr., 'The origin of G. N. Lewis's theory of the shared pair bond,' *Stud. Hist. Phys. Sci.*, 1971, *3*, 343–376; idem, 'Irving Langmuir and the "Octet" theory of valency,' *Stud. Hist. Phys. Sci.*, 1974, *4*, 39–87; idem, 'The Lewis-Langmuir theory of valence and the chemical community, 1920–1928,' *Stud. Hist. Phys. Sci.*, 1975, *6*, 431–468; idem, 'G. N. Lewis's views on bond theory 1900–16,' *Br. J. Hist. Sci.*, 1975, *8*, 233–239. Emil Fischer, doyen of structural chemists, had perceptively noted: 'Wöhler's famous synthesis of urea in 1828 was the starting point for the glorious evolution which for many decennia gave organic chemistry a leading part in the development of chemical theories. But this era seems to be drawing to a close. The almost obvious view that the one-sided study of carbon compounds cannot suffice to elucidate the nature of chemical processes in all its aspects had again won some measure of acceptance, and general chemistry, in closer association with physics, has been diverted back into the paths which it was following at the beginning of the nineteenth century under the guidance of Berzelius, Gay-Lussac and Davy.' From his 'Syntheses in the purine and sugar group' (1902), pp. 21–35 in Nobelstiftelsen, Stockholm, *Nobel lectures . . . chemistry, 1901–1921* (Amsterdam, 1966), pp. 21–22.

78. The term *covalent* was introduced by Irving Langmuir in 'The arrangement of electrons in atoms and molecules,' *J. Am. chem. Soc.*, 1919, *41*, 868–934.

79. Linus Pauling, *The nature of the chemical bond and the structure of molecules and crystals* (Ithaca, N.Y., 1939), p. 3. For a recent recollection of the enormous impact of Pauling's text, see Max Perutz, 'Memorable books,' *New Scient.*, 1977, *76*, 795–796.

that diphtheria toxins, employed extensively by Ehrlich, were peculiarly complex mixtures, and Ehrlich rejoined that Arrhenius's and Madsen's tetanolysin was 'a downright *méchante* poison. It is so labile, that one finds oneself continually between the Scylla of disintegration and the Charybdis of insufficient [*ungenügender*] bonding.'[80] This issue too may be resolvable by recourse to the later bonding model. Antibody-antigen affinity—which is subject to mass action—depends upon a variety of nonspecific interactions: electrostatic, or ionic, interactions between oppositely charged groups; hydrogen bonding; hydrophobic interactions, which contribute most to stability; and, van der Waals forces (interactions between outer orbital electrons of neighboring molecules). Where antibody-antigen fit is extensive the area on which these forces can act is large, and the total energy of the complex is low, that is, it is stable.[81] The picture that emerges incorporates physicochemical forces favored by Arrhenius acting in harmony with Ehrlich's dictum that bodies do not interact unless they are connected.

The scientific basis for the controversy and the problems that confronted and perplexed Ehrlich's and Arrhenius's generation dissipated for their pupils. For members of the next generation, often trained in both chemical schools, the distinctions drawn by their teachers no longer seemed so hard and fast. Later investigators accomplished the task of defining the relation between molecular structure and kinetics and thermodynamics. The change was gradual, in part due to the separation of the communities of physical and organic chemists. As Leonor Michaelis wrote at the death of Ostwald: 'He [Ostwald] taught . . . that the task of the chemist was not only the preparation and analysis of new compounds, but also the establishment of the physical laws generally underlying chemical reactions. It took quite a time for the older generation of chemists to appreciate the fact that something could be achieved in chemistry, even though no new compound had been prepared.'[82] Michaelis's own research—he was a protégé of Ehrlich—and that of Arrhenius's student Hans von Euler are prime examples of the fertility of this newer biochemistry of the 1920s and '30s.[83] That middle

80. Commentary on Arrhenius's 'Serumtherapie' (n. 58), p. 673. Also see Ehrlich's 'Giftcomponenten' (n. 66), p. 349.

81. Ivan M. Roitt, *Essential immunology*, 3d ed. (Oxford, 1977), pp. 9–16; Linus Pauling, 'Nature of forces between large molecules of biological interest,' *Nature*, 1948, *161*, 707–709.

82. L. Michaelis, 'Wilhelm Ostwald,' *Scient. Mon., Lond.*, 1932, *34*, 566–570, p. 568.

83. Michaelis, a pioneer in several fields, is today remembered largely for his eponymous equation of enzyme kinetics: Leonor Michaelis and Maud L. Menten, 'Zur Kinetik der Invertinwirkung,' *Biochem. Z.*, 1913, *49*, 333–369. This work also finds application in a variety of physiological, including

ground had eluded their teachers. Ehrlich, enamored by structure and versed in the techniques of organic chemical substitution and synthesis, concentrated on the complicated molecules involved in the immune response. Arrhenius, at home with the statistical molar explanations of physical chemistry, sought to describe the gross physical properties of the reaction system; questions of the structure of the constituents were of only incidental and peripheral concern.

Their debate was moribund by 1910 and this intellectual synthesis cannot have decided the question. One must take into account several institutional and professional factors. Arrhenius's pleas for the application of physical chemistry to biology were, indeed, heeded by several investigators. Michaelis was sensitive to the problems, as were such other medically trained scientists as Jacques Loeb and Karl Landsteiner. (All three eventually found professional homes at the Rockefeller Institute for Medical Research in New York.) These men did not hold Arrhenius's passionate intellectual attachment to the primacy of electrolytic dissociation, and they were more cognizant than he of the complicating factors inherent in physiological regulatory mechanisms.[84] By contrast, many if not most investigators in immunology were singularly unmoved by Arrhenius's studies. Largely trained as pathologists, bacteriologists, or clinicians, they could not appreciate a physical chemist's incursion into their preserve. Arrhenius's exasperation with medically trained biochemists was probably an expression of his sense of futility in addressing this audience.[85] Even *Immunochemistry*, an important work by any standard, made a less than major impact.[86]

Immunology's raison d'être for practitioners was serum therapy. Effective serums against the destructive exotoxins of diphtheria and tetanus, due in large part to Ehrlich's efforts, for a time seemed to provide an antidote to the therapeutic nihilism professed by leading physicians in the late nineteenth century. In expectation that antibacterial measures might be developed against a wider class of ailments, physicians flirted with such fashions

immunological, reactions. Von Euler applied Ehrlich's antigen-antibody dual affinity model to enzyme-substrate interactions: Fruton, *Molecules and life* (n. 6), p. 80.

84. For background see H. L. Hamburger, 'Zur Geschichte und Entwicklung des Physikalisch-chemische Forschung in der Biologie,' *Int. Z. phys.-chem. Biol.*, 1914, *1*, 6–27.

85. Arrhenius, *Quantitative laws* (n. 49), p. vi.

86. See H. Gideon Wells's review of *Immunochemistry* in *J. Am. chem. Soc.*, 1908, *30*, 650–652. Mazumdar has concluded, 'Gruber and his students seem to have been alone in finding it sensational.' From Mazumdar, 'Landsteiner' (n. 1), p. 375. A further factor in the lack of appeal was undoubtedly the appeal of colloidal explanations for the phenomena of agglutination, bacterial precipitation, hemolysis, and the like.

as Sir Almoth Wright's vaccine therapy. Arrhenius's formulations, as Nernst had so readily charged, did not address the practical issues of immunization. Nor did they yield a satisfying account of the remarkable specificity of the immune response. The genesis of Ehrlich's side chain theory was the elucidation of just such issues, and the specificity of the immune response certainly counted heavily for its popularity.

A second factor was that Ehrlich's theory, like the chemical bonding it described, was tenacious. The pathologist Ludwig Aschoff wrote an immensely popular exposition of the theory in 1905,[87] and Ehrlich's Frankfort institute turned out scores of workers versed in its byzantine complexities. Testimonials, such as August Wassermann's claim that he drew inspiration for his diagnostic test for syphilis from the side chain theory, no doubt enhanced its standing.[88] Prior to the First World War the theory and its peculiar terminology were entrenched as medical orthodoxy, as a paradigm, if you will,[89] especially in Central and Eastern Europe. Its defense became something of a cottage industry, and in German-speaking lands, at least, to challenge its foundations could endanger one's career. Outside the German *Sprachgebiet*, however, Ehrlich's detractors were numerous.[90]

Finally, on the scientific side, Ehrlich's theory, in distinction from Arrhenius's, attempted to explain all known phenomena of humoral and cellular immunity. Buried in the side chain theory were several powerful and adaptable concepts which have persisted long after the chemical considerations Ehrlich employed passed from fashion.[91] A recent conference on

87. Ludwig Aschoff, *Ehrlich's Seitenkettentheorie und ihrer Anwendung auf die künstlichen Immunisierungsprozesse* (Jena, 1905). Admirers produced numerous tracts of variable quality, e.g., P. Schatiloff, *Die Ehrlichsche Seitenkettentheorie erläutert und bildlich dargestellt* (Jena, 1908).

88. A. Wassermann, 'Paul Ehrlich,' *Münch. med. Wschr.*, 1909, *56*, 245–247. Bela Schick recalled that at the beginning of the century at the Vienna Serological Institute, Aschoff's book was standard reading. B. Schick, 'Ehrlich and problems of immunity,' *Bull. N.Y. Acad. Sci.*, 1954, *59*, 182–189.

89. E.g., Kuhn, *Structure of scientific revolutions* (n. 5), p. 10.

90. The young Landsteiner, apparently, found himself a hapless victim of the Ehrlich-Gruber controversy: Mazumdar, 'Landsteiner' (n. 1), p. 480–486. Ehrlich's theoretical schemes were never very influential in Francophone countries. In fact, Ehrlich's major advocate in the French scientific community was the Rumanian-born microbiologist Constantin Levaditi. See Levaditi's 'L'immunité d'après la théorie des "chaines latérales," ' *Presse méd.*, 1900, *ii*, 339–343; 1901, *ii*, 109–113. Franco-German animosities tainted the reception of the theory, and during the First World War the jingoist tract *Les Allemands et la science*, edited by Gabriel Petit and Maurice Leudet (Paris, 1916), used Ehrlich as a main object of derision. I want to thank J. S. Fruton for bringing this reference to my attention.

91. See, for instance, W. H. Manwaring, 'Renaissance of pre-Ehrlich immunology,' *J. Immun.*, 1930, *19*, 155–163. One might compare Ehrlich's speculations with those of a mid-twentieth-century theoretical immunologist, Sir Macfarlane Burnet. Ehrlich's side chains are similar to Burnet's idea of 'adaptive enzymes' and Ehrlich's dictum *horror autotoxicus* and Burnet's concept of the self-marker carry the same import. Nevertheless, for Burnet's offhand and unfavorable assessment of Ehrlich's concepts, see his *The integrity of the body: a discussion of modern immunological ideas* (Cambridge, Mass.,

'Membranes, receptors, and the immune response' (La Rabida–University of Chicago Institute, 23–24 September 1979), held in commemoration of the eightieth anniversary of the side chain theory, testifies to a continued awareness by active investigators of Ehrlich's contributions.

Conclusions on Styles

The language in which Ehrlich and Arrhenius expressed their adherence to one or another scientific style consisted of a series of analogies. Consequently, their debate illustrates that when investigators approach a new field they tend to rely on analogies to known systems, and are subject to an unavoidable tendency to incorporate the false and misleading along with the true or heuristic aspects of the analogy.[92] Ehrlich, then, was apt to assume (incorrectly, as it happened) on the basis of highly equivocal evidence that there existed a multiplicity of antibody-specific complements; this belief fitted his conception of stereospecific intermolecular bonding. Similarly, Arrhenius, though he cautiously denied the identity of antibodies and antigens with weak acids and weak bases, tended incautiously to extend the analogy.

The utility of the physicalist and structural styles for a given problem may hinge on the suitability of the analogies chosen and on their judicious application. These analogies or metaphors—Ehrlich and Arrhenius were not always clear as to which they used—allow one to apply a tested scientific vocabulary to the description of new phenomena. Lindley Darden and Nancy Maull have recently examined several theories that bridge scientific fields, and they have drawn attention to the role of shared vocabularies in linking different branches of inquiry.[93] One might consider the immunochemistries of Arrhenius and Ehrlich as examples of Maull's 'interlevel theories.'[94] The controversy was fueled by a lack of an agreed upon

1962), pp. 9–10, 39. Cf. H. S. Baar, 'From Ehrlich-Pirquet to Medawar and Burnet,' *J. Maine med. Ass.*, 1963, *54*, 209–214.

92. See, for example, Thomas S. Kuhn, *The essential tension: selected studies in scientific tradition and change* (Chicago and London, 1977), pp. 297–298.

93. Lindley Darden and Nancy Maull, 'Interfield theories,' *Philosophy Sci.*, 1977, *44*, 43–64; Nancy L. Maull, 'Unifying science without reduction,' *Stud. Hist. Phil. Sci.*, 1977, *8*, 143–162. They have especially looked at the relationship between 'biological' and 'physico-chemical' speculations.

94. Maull (n. 93), pp. 160–161: 'While an interfield theory, the more general type, can be said to *explain connections between fields, an interlevel theory explains the connections between fields* ordered as descriptive levels. While the generation of an interfield theory is associated with a shared problem, the genesis of an interlevel theory is associated with a problem-shift characteristic of fields ordered as descriptive levels.' On issues of analogy, metaphor, and conceptual change see Donald A. Schon, *Displacement of concepts* (London, 1963).

level of chemical description from which one might derive concepts and techniques.

Exacerbating the conflict was the fact that Arrhenius and Ehrlich did not even share a standard from which they could evaluate their theories. Occam's razor in this case was a double-edged sword. Though Arrhenius frequently invoked simplicity and economy, Ehrlich's sense of economy was quite different, derived from the 'animal economy,' that is, physiology. In the course of his second Harben Lecture Ehrlich catalogued the variety of active substances known to circulate in the bloodstream; each, he noted, had several distinct functions. 'Although in some quarters the endeavor is made to reduce everything to the simplest imaginable form,' he concluded, 'I believe that such a rudimentary way of looking at things is not justified by the appreciably complex character of natural phenomena and vital processes. . . .' The replacement of concepts of immunity, he maintained, 'takes place always by the substitution of a complex conception in place of a simple one. . . .'[95] Nature's ultimate immunological simplicity remains elusive, and Ehrlich might be gratified by subsequent immunological theorizing. Today's cellular immunologist must contend with an ever increasing family of functionally specific immunoregulatory cells (T lymphocytes). Yesterday's relative simplicity has yielded to a complicated bureaucracy of interacting, identically looking cells.

Ehrlich's and Arrhenius's predisposition to a particular style of thought guided but did not necessarily dictate the nature of their explanations. Ehrlich hesitated for nearly a decade before applying the side chain theory to drug action. Noting that many drugs are easily extracted from tissues with organic solvents, he distinguished the union of most drugs with cells —a feeble saltlike union, not unlike that of Arrhenius's weak acids and weak bases—from the chemical union he posited between protoplasm and foodstuffs or toxins. Only later, under the influence of the work of John Newport Langley and of his own studies on trypanosome infections, did Ehrlich change his mind and postulate that cells have chemoreceptors as well as nutriceptors.[96] The same set of principles, namely, those derived

95. Paul Ehrlich, *Experimental researches on specific therapy* (London, 1908), in *Collected papers* (n. 7), III, 106–117, p. 114. Cf. Northrop (n. 73).

96. This frequently unappreciated division between Ehrlich's immunological and pharmacological thinking has been treated by John Parascandola, 'The controversy over structure and activity relationships in the early twentieth century,' *Pharmacy Hist.*, 1974, *16*, 54–63; John Parascandola and Ronald Jasensky, 'Origins of the receptor theory of drug action,' *Bull. Hist. Med.*, 1974, *48*, 199–220. Also compare Ehrlich's 'The relations existing between chemical constitution, distribution, and pharmacological action,' in *Gesammelte Arbeiten* (Berlin, 1904); in *Collected papers* (n. 7), I, 596–618, with

from the laboratory practice of organic chemistry, prompted both his initial hesitation and later conviction.

The debate examined above focused on a perennial issue: does a biologically active molecule—be it antigen, antibody, drug, enzyme, hormone—function by uniting chemically with a cellular constituent? If so its action is a matter of molecular structure. Or is its action largely determined by its physical properties? These positions are, perhaps, two sides of the same coin: by altering molecular configuration or conformation one may alter physical properties as well as chemical reactivity. In the history of biology and chemistry, substances have been categorized sometimes by structural similarities and at other times by resemblances in physical properties. The tension between physicalists and structuralists nonetheless plays a central role in several speculative fields of science.[97] William James once appropriately suggested:

All [thinkers] follow one analogy or another; and all analogies are with some or other of the universe's subdivisions. Every one is nevertheless prone to claim that his conclusions are the only logical ones, that they are necessities of universal reason, they being all the while, at bottom, accidents more or less of personal vision which had far better be avowed as such; for one man's vision may be much more valuable than another's. . . . Different men find their minds more at home in very different fragments of the world.[98]

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his 'Ueber den jetzigen Stand der Chemotherapie,' *Ber. Dt. chem. Ges.*, 1909; in *Collected papers* (n. 7), III, 150–170.

97. One clear example would be contemporary theories of narcosis, i.e., the mechanism of action of anesthetic agents. For the range of speculation in this field, see Louis S. Goodman and Alfred Gilman, eds., *The pharmacological basis of therapeutics*, 5th ed. (New York, 1975), pp. 56–59.

98. William James, *Essays in radical empiricism and a pluralistic universe*, ed. Ralph Barton Perry (New York, 1971), pp. 126–127; also see pp. 131–132.