# Species and Specificity

## An Interpretation of the History of Immunology

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CAMBRIDGE
UNIVERSITY PRESS

PUBLISHED BY THE PRESS SYNDICATE OF THE UNIVERSITY OF CAMBRIDGE
The Pitt Building, Trumpington Street, Cambridge, United Kingdom

CAMBRIDGE UNIVERSITY PRESS
The Edinburgh Building, Cambridge CB2 2RU, UK
40 West 20th Street, New York NY 10011–4211, USA
477 Williamstown Road, Port Melbourne, VIC 3207, Australia
Ruiz de Alarcón 13, 28014 Madrid, Spain
Dock House, The Waterfront, Cape Town 8001, South Africa

http://www.cambridge.org



First published 1995
First paperback edition 2002

*A catalogue record for this book is available from the British Library*

*Library of Congress Cataloguing in Publication data*
Mazumdar, Pauline M. H. (Pauline Margaret Hodgson), 1933–
Species and specificity: an interpretation of the history of
immunology / Pauline M. H. Mazumdar
p. cm.
Based on the author's thesis (Ph.D. – Johns Hopkins University,
1976)
ISBN 0 521 43172 7 (hardback)
1. Immunology – History. I. Title.
[DNLM: 1. Allergy and Immunology – history. 2. Species
Specificity. QW 511.1 M476s 1994]
QR182.M39 1994
574.2'9'09–dc20
DNLM/DLC
for Library of Congress
93-31219 CIP

ISBN 0 521 43172 7 hardback
ISBN 0 521 52523 3 paperback

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# Introduction

Species and specificity are the concepts that lie at the heart of the modern science of immunology. They make possible the modern immunological understanding of the self and its individuality, of the self's recognition of the other, and of the biological processes that constitute the relationship between them. As concepts, species and specificity go back to the classical roots of Western thought in the work of Aristotle, and they have played a central part in the biological sciences at least since the eighteenth century, with its flowering of classification systems in all the sciences, but especially in the science of botany.

It is the reappearance of the botanical dispute about the nature of species in the work of the bacteriologists, and after them in the work of the immunologists, immunochemists and blood group geneticists, that I shall discuss in this book. In the course of this controversy, five generations of scientific protagonists made themselves aggressively plain. Their science was designed only in part to wrest an answer from nature. It was at least as important to wring an admission of defeat from their opponents – and these were opponents that never admitted defeat.

A controversy is the most useful of all forms of discourse for the historian. Engaged in it, protagonists display themselves with a frankness and enthusiasm that they would never otherwise have needed to make public. Concepts, as Geoffrey Lloyd has pointed out in the case of Greek science, become more explicit when they are part of a debate, a contest with an antagonist.[1] In a world where underlying assumptions are all agreed upon, they may well remain unconscious or unspoken: a single, all-encompassing paradigm is likely to be invisible from within, and undetectable from outside.

There is more: a controversy helps define a style of thought by comparison with its opposite, that which it is not. For the historian, partic-

1 Geoffrey E. R. Lloyd, *Demystifying Mentalities* (Cambridge: Cambridge University Press, 1990), 57–60.

ularly the historian of science or medicine, the temptation is always to compare the thought of the past with that of our own time. How could *they* have thought that, when *we* can see it doesn't work? Even if we are not as naive as all that, our own interpretation of scientific phenomena may be our only available yardstick: we are left to try to recognize the specificity of the past in terms of self and not-self, to make use of an immunological metaphor. A controversy, however, lets us see the past in terms of its own possibilities: if we know of the alternatives available to the protagonists, we can understand them in something much closer to their own terms, so that we may be less inclined intuitively to push our science forward as the model that they failed to grasp.

The controversy treated in this book was both synchronic and diachronic: it lasted for one hundred years or more, and at any one period, it involved many individuals. Its two teams of thinkers fought over the fundamentals of their science from the mid-nineteenth century to the mid-twentieth. Five generations of teachers and students, grandstudents, and great-grandstudents loyally maintained their *diadoche* as their science metamorphosed from botany through bacteriology to immunology. The group that I have called the pluralists insisted on the separation and definition of species, and the others, the unitarians, on the continuity of nature. For each science in turn, the problem of species and their definition came close to being the essential problem of the science. The two opposing groups were established long before the rise of immunology, but it is for that science that this controversy has proved to be so revealing.

In the years before 1957, when the clonal selection theory of MacFarlane Burnett came to replace serology at the centre of the stage, the applications of serology in medicine and public health were the motor that drove both practice and the theory that derived from it. The problems of species and specificity were the core problems of both research and practice in immunology. I present this five-generation controversy as a key to the structure of immunological thought as it evolved in the first half of the twentieth century.

Kant was not the first to point out that students of nature fall into two groups. The first, the more speculative, are always on the watch for the unity underlying the diversity of nature, and the second are those who, often more practical or empirical, try to differentiate nature, to accentuate its diversity, to divide into species rather than to unify into genera. Kant himself, he says, gives each kind of thinking its due. The principle of homogeneity is balanced by that of specification, and they are joined by the principle of continuity, which connects the two into a systematic unity. *Datur continuum formarum,* he says, all species border on one another, admitting of no transition *per saltum.* This is the transcendental *lex continui in natura,* a maxim of scholastic logic. But being transcendental, it is a law of the mind only. In experience, species are actually clearly divided, and constitute a *quantum discretum.*

The principles of systematic unity, then, are placed in the order manifoldness, affinity, unity: reason passes beyond experience as it seeks for unity in knowledge.[2] For Kant, the unity is in the human mind, nature itself is manifold. It is to this unifying effort of the human mind that he refers in his famous *Satz,* that each science is scientific only in proportion to the amount of mathematics in it. It is by mathematics that manifoldness in nature becomes continuity in the mind. Whether the unity is to be found in nature as well as in the mind is a different question. Another of Kant's scholastic maxims, *Entia praeter necessitatem non esse multiplicanda,* presumes that it is: chemists, he says, suppose that a step forward was made when the many salts were divided into only two genera, acids and bases; and they are now seeking to show that even these are two varieties of a single fundamental material. They suppose that the unity of reason is justified by the unity of nature itself.

Kant's words suggest that he himself belongs to the group that looks for unity and continuity in thought and in things, but the form of his thought suggests the opposite. It is built up of distinctions and dichotomies and sharp boundaries. His division of the acts of the understanding into categories and those of the reason into regulative ideas performs for the mind what the natural historian of the eighteenth century performed for nature. Linnaeus's division into class, order, genus, species, and variety is a system that divides nature into categories as Kant's system does thought. Kant's categories of the understanding are somewhere near the genera; his regulative ideas correspond to the orders of Linnaeus's system. Both ultimately derive from the five levels of classification of scholastic logic: *genus summum, genus intermedium, genus proximum, species,* and *individuum.*[3]

The problem of species in medieval metaphysics and the essentialist logic with which it was connected are directly related to Linnaeus's classification through the work of the seventeenth-century

2 Immanuel Kant, *Kritik der reinen Vernunft* (1781), translated by Norman Kemp Smith (1929) (Toronto: Macmillan, 1965), 532–549: "The regulative employment of the ideas of pure reason" (pp. 540 ff.).

3 Frans A. Stafleu, *Linnaeus and the Linnaeans: The Spreading of Their Ideas in Systematic Botany* (Utrecht: Oosthoek 1971), 26, 32 (refers only to Linnaeus: the comparison with Kant is mine!).

botanist Andreas Caesalpino.[4] Caesalpino suggested that the essence of a plant lay in the parts serving the functions of its vegetative soul, that is, in growth and reproduction. A truly essentialist classification should therefore take as its *fundamentum divisionis,* the reproductive organs of the plant. The *differentiae* at each of the successive dichotomies of which the classification consists should ideally all refer to this original *fundamentum divisionis.* This, which is Linnaeus's method, and that of the botanists who followed him, is precisely that of the definition *per genus et differentiam* of scholastic logic. The medieval metaphysical problem has become the problem of identifying and classifying plants.

In an essay of 1931, the psychologist Kurt Lewin contrasted the kinds of concept typical of the Aristotelian and the Galilean modes of thinking. Lewin describes as Aristotelian the division of objects into well-defined classes and the use of antithesis and dichotomy; he contrasts this with the unity of the physical world described by Galileo, in which dichotomy and antithesis are replaced by continuity, gradation, and fluid transitions, the class concept by the series concept.[5] Following Lewin, the Ansbachers compared the psychologists Alfred Adler and Sigmund Freud: Freud analyzes, dissects, dichotomizes; he splits mind into death wish and sex drive. Adler rejects such dichotomies, denies the existence of specific categories of mental disease, stresses the unity of the neuroses. He keeps his technical terminology to a minimum, in contrast to Freud, who developed an elaborate vocabulary with many named entities. Adler is a "field theorist," Freud is a "class theorist."[6] They represent the same two groups of students of nature that Kant described in 1781: the field theorist is always on the watch for unity, the class theorist for hidden heterogeneity.

The Linnaean botanists, Aristotelians *sensu stricto,* are Aristotelians in this metaphorical sense too. Their botany is a search for *differentiae* with which to mark off species from each other; existing classes are split up, previously unnoticed dichotomies are brought to light, and species boundaries are rearranged accordingly. When the boundaries are difficult to fix in nature, they are fixed instead by definition. Species differ

4 Philip R. Sloan, "John Locke, John Ray and the natural system," *J. Hist. Biol.* 5(1972): 1–53.

5 Kurt Lewin, "The conflict between Aristotelian and Galilean modes of thought," *J. Gen. Psychol.* 5(1931):141–177; and in Kurt Lewin, *A Dynamic Theory of Personality: Selected Papers,* translated by D. K. Adams and K. E. Zener (New York, N.Y.: McGraw-Hill, 1935).

6 Heinz Ludwig Ansbacher and Rowena R. Ansbacher, *The Individual Psychology of Alfred Adler: A Systematic Presentation in Selections from His Writings* (New York, N.Y.: Basic Books, 1956).

sharply from each other, if they are "good" species – if the botanist, that is, is good.

Linnaean botany had its opponents even in the eighteenth century, especially in France. In 1809 there appeared Jean Baptiste de Lamarck's *Philosophie Zoölogique*, in which classes, orders, families and genera are called *parties de l'art*, or devices introduced by art for human convenience, artificially dividing up nature's continuous series, a series that begins with *Monas* and ascends by infinitesimal differences to man.[7] The lines of demarcation are arbitrary for there are no gaps in nature.

In Germany, Matthias Schleiden seems to have been among the earliest to take up a position opposed to that of systematic botany. His cell theory provided a common lawfulness, a unity underlying the diversity of Linnaean species. In his *Textbook of Botany as an Inductive Science* of 1844, he attacked his Linnaean contemporaries, using Kant's critical philosophy and the heuristic maxims, and with the help of the Kantian philosopher J. F. Fries. Kant's heuristic maxim of unity was one of the regulative ideas of the reason, a category at the highest and most general level of the mind's activity. Although Schleiden found the transcendental *Naturphilosophie* pernicious and absurd, he, like the *Naturphilosophen*, took the search for unity in nature's diversity to be the basic principle of human reason.

It was this desire for unity in scientific thought and the search for it in nature that Schleiden passed on to his otherwise rather disrespectful student Carl von Nägeli. Like Schleiden, Nägeli attacked the Linnaeans, though as a young man he himself had begun by trying to define the species of unicellular algae. Nägeli was a classical field theorist: his unitarianism is a constant feature in everything he wrote from 1853 onwards. In each of the areas in which he worked, it is the *lex continui in natura* that is his leading maxim. He applies it in his phylogeny, which is close to that of Lamarck, in his work on the fine structure of living matter, in his theory of fermentation, in his bacteriology, and in his theory of knowledge. Each of these fields is united to each of the others in a continuous network of thought. *Kontinuität* and *quantitative Abstufung* are the terms he uses to describe the relations of things to each other: there are no sharp boundaries between species. In the case of the "lower fungi," the bacteria, there are not even separate species.

Nägeli's opponent among the Linnaeans was the botanist Ferdinand Cohn of Breslau. Cohn, the class theorist, developed a new classification of simple plants, beginning like Nägeli from an interest in unicellular algae. He then moved on to the bacteria, classifying them along

7 H. Elliott, "Introduction," to *Zoological Philosophy, etc. by Jean-Baptiste de Lamarck*, translated and introduced by H. Elliott (New York, N.Y.: Hafner, 1963), xvii–xcii (p. xxvii).

Linnaean lines by dividing them into four tribes with six genera. His species were mainly defined morphologically, though he recognized that this was probably only a temporary means of classification. The size of the bacteria made classification difficult, and for a Linnaean botanist the absence of special reproductive organs and the difficulty of observing the growth cycle made them especially difficult to deal with. But Cohn was sure that the different species would eventually be properly defined. Where Nägeli saw *Kontinuität,* Cohn saw differentiation: when our microscopes were better, the *differentiae* would come to light. It was because of Cohn's attitude to species that the young Robert Koch wrote to him and not to Nägeli with his offer to demonstrate to him the complete life cycle of the anthrax bacillus.

Koch very quickly became a brilliant bacteriologist whose new morphological technology of stains, solid media, and optical improvements lifted the identification of bacterial species onto a different plane. His adoption by Cohn and his very rapid rise to fame and power within the framework of the new German state set the course of medical bacteriology for generations towards a definition of species of bacteria and their matching species of disease. The growth of Koch's professional power and its institutionalization, together with the active support of the state, first in the Reichsgesundheitsamt in Berlin, and later in the Institut für Infectionskrankheiten, produced a group of enthusiastic students and co-workers, for whom a belief in absolute specificity was an essential mark of group loyalty.

The two kinds of thinking now came into violent conflict. In 1880, in a publication of the Reichsgesundheitsamt, Koch and his students attacked the representatives of *Kontinuität,* who included not only Nägeli himself and his students in Munich but also Louis Pasteur in Paris, and attacked them with extraordinary violence. Nägeli and his group replied, but it was soon clear that they had been defeated. Although this defeat and the enormous growth of Koch's influence ensured that the definition and separation of species of bacteria were generally accepted, Nägeli's thinking was not completely expunged. It continued to live in the minds of the students he had trained. Nägeli's principles of unity, continuity, and *quantitative Abstufung* are found again in the work of Max Gruber.

For Schleiden's generation, and for Nägeli in his earlier days, specificity had been a botanical problem. For Koch and the older Nägeli, it was a problem of bacteriology. For the next generation, it became a problem of immunology: bacterial species, in the absence of visible, morphological differentiae, might be defined by their reaction with specific antisera. Richard Pfeiffer, as Koch's student, maintained that they could be: Gruber, the student of Nägeli, maintained that the specificity of antisera was a matter of *quantitative Abstufung*. The conflict of the earlier generation was repeated by the next: Gruber attacked Koch's student Pfeiffer, and later, as a matter of course, Koch's student Paul Ehrlich.

In the work of Paul Ehrlich, the characteristics of the Linnaean thinker are very well marked. It is all the more interesting that they should be, for Ehrlich had no direct contact with Linnaean botany, apart from his medical training. His thinking can be seen growing along these lines in his juvenile work on dyes, where his use of classes and dichotomy is already well developed. In 1880, in his early work on white blood cells, he treats them exactly as if they were botanical species. It is not surprising that Ehrlich should have been as certain as Koch of the absolute nature of specific differences.

It is this absolute specificity that sets the style of Ehrlich's theory of immunity. Species specificity in immunology is explained by the specificity of affinity chemistry: his receptor theory, which originated as a chemical explanation of dye specificity, was transferred first to immunity and later to chemotherapy. Ehrlich's loyalty to Koch and to the Koch group to which he belonged was no more marked than the loyalty of Max von Gruber to his teacher Carl von Nägeli. Gruber's attack on Koch's specificity passed over to an attack on Ehrlich's specificity and was inherited in turn by Gruber's student Karl Landsteiner, who himself later attacked Ehrlich.

For Landsteiner, the conflict took place in the field of immunochemistry. Very early in his career, Landsteiner began using the diagnostic terms of the field thinker, *Kontinuität* and *quantitative Abstufung*, terms that appeared so often in Nägeli's writing. For this generation the personal struggle, in which loyalties and methodological styles were combined, was reflected in the larger conflict that was taking place between physical chemistry and the affinity chemistry of the structural organic chemists. The new and exciting field of colloid chemistry, the youngest branch of physical chemistry, seemed to suggest that chemical specificity might play no part at all in the reactions that took place in the living organism.

Ehrlich's chemical receptor theory seemed at first to have gone down before the physical or almost-physical conception of antigenic specificity. But Ehrlich's theory was strongly institutionalized: state serum institutes across the world worked along the lines he had laid down, and his hold over the field of practical serology did not die with him. In one area of immunology the receptor theory itself was able to survive intact: this was the field of blood group serology and blood group genetics. Here the receptor theory of immune specificity and the unit-character theory of genetics united to give a picture of absolute specificity that persisted long after both the unit-character theory and the receptor theory had disappeared from their original applications. The receptor theory in blood grouping remained unchallenged until the late 1940s, when there arose a new champion of *Kontinuität,* in Landsteiner's last and youngest student, Alexander Wiener. Wiener's long and bitter controversy with Robert R. Race and Ronald A. Fisher about the terminology for the Rhesus blood group system is the last act in this agon. It has not been resolved.

The conflict has been going on now for five generations. In each generation, new actors have arisen to play the same parts, often in the same words. Each of them has represented not only his own attempt to solve a particular scientific problem, but has acted as spokesman for his group and student of his teacher. This was particularly true of the Koch–Ehrlich group in Germany, where the social and institutional power of their many chairs and directorships was backed by the power of the journals they founded and edited. Landsteiner, excluded from this alliance by his well-known opposition to Ehrlich, was effectively excluded from professional power in the German-speaking world.

In the earlier part of this history, the part played by Kant's heuristic maxim of unity as the model for Schleiden's thought is easy enough to see. Schleiden himself leaves us in no doubt about it. The part played by the physicist-philosopher Ernst Mach later on in the story is not so clear. The statements Mach made about the nature of scientific thought are those of a seeker for unity far more whole-hearted than Kant. There is little lingering Aristotelianism here: in fact, the distinction between Aristotelian statics and Galilean dynamics, one of the sources of Kurt Lewin's essay which was cited earlier, comes from Mach's history of mechanics.[8] The function of science, in Mach's view, is to generalize and simplify, to subsume experience under progressively fewer and simpler laws. This principle of science he calls the principle of the economy of thought.[9] It first appeared in print in 1872, in *Die Geschichte und die Würzel des Satzes von der Erhaltung der Arbeit.* The principle of continuity, he says, which everywhere pervades modern inquiry, simply prescribes a mode of conception that conduces in the highest degree to the economy of thought.[10]

8 Ernst Mach, *Die Mechanik in ihrer Entwicklung: historisch-kritisch dargestellt* (1883), translated by Thomas J. McCormack (Chicago, Ill.: Open Court, 1893).

9 Ernst Mach, *Die Leitgedanken meiner naturwissenschaftlichen Erkenntnislehre und ihre Aufnahme durch die Zeitgenossen,* und *Sinnliche Elemente und naturwissenschaftliche Begriffe, Zwei Aufsätze* (Leipzig: Barth, 1919), 4.

10 Mach, *Mechanik* (1883) (n.8), 490.

As a philosopher, Mach was the mouthpiece of the scientists of his time, particularly of the physical scientists, in whose writing the same emphasis on simplicity and continuity is often to be found. He himself saw this as an essential part of being a philosopher of science, a representative of scientific modes of thought in philosophy. Among physiologists, interest in Mach was widespread, but in many cases those who cited him were more concerned with the biological side of his thought, the sensationalist epistemology, than in the principles of economy and continuity. His influence on the broader cultural life of Vienna in the early decades of the twentieth century was also enormous. Simplicity and economy formed part of the *neue Sachlichkeit*, the outpouring of positivistic thought from science into art and literature that took place in those decades.

In many ways, Mach as the mouthpiece of contemporary physical science codifies and parallels much that is to be found in the writings of Karl Landsteiner, and at first sight, in view of the opportunities for contact in Vienna, it is hard to believe that they were completely independent. But Landsteiner never actually cites Mach, and it is going too far, where there are no such citations or other evidence, to speak of a direct influence, particularly when the direct influence of Gruber is so clear. The case is still an open one, however: the verdict so far is *ignoramus*, "not proven."

It is on the life and work of Karl Landsteiner, extending as it does over so many years of changing thought in immunology, that I have focused this book. Like his predecessors, Carl von Nägeli, Max von Gruber, and Hans Buchner, and his successor, Alexander Wiener, Landsteiner the unitarian was on the losing side. Specificity and pluralism, the legacy of Robert Koch and Paul Ehrlich, were entrenched in the work of the state serum institutes, and it was they, with their practical importance in the world of public health and clinical medicine, who made the rules in the Europe of Landsteiner's day. Only in the protected environment of the Rockefeller Institute in New York was Landsteiner to be free of this powerful opposition. In the course of his twenty years at the Rockefeller Institute, he was both productive and greatly admired, even to the extent of winning a Nobel prize. But he was never to be a happy man: his personal experience was one of failure.