Darwinian Overtones: Niels K. Jerne and the Origin of the Selection Theory of Antibody Formation

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INTRODUCTION

From "Seitenketten" to Clonal Selection: Three Generations of Theories of Antibody Formation

How are antibodies produced? This remained the central question in immunology for more than half a century after Emil von Behring and Shibasaburo Kitasato's discovery in 1890 of humoral antibodies in the blood serum. Three generations of theories have been proposed to account for their formation.[1] First, Paul Ehrlich suggested in 1897 that all cells in the body carry "Seitenketten" (side-chains) for the adsorbance of nutrients. Certain foreign substances, like toxins, were thought to resemble nutrients and to be recognized by the specific side-chains; the cell then, Ehrlich thought, produced an excess of specific side-chains, which were released into the bloodstream as antibodies to neutralize the toxin.[2]

Ehrlich's preformation theory fell into disrespute with the detection of an increasing number of chemical substances, and particularly through Karl Landsteiner's experiments with synthetic haptens in the 1920s.[3] Evidence accumulated to the effect that almost any foreign substance is an antigen to which the body can produce specific antibodies; it was considered impossible that the

1. See Arthur Silverstein, *A History of Immunology* (San Diego: Academic Press, 1989), chap. 4.

2. Paul Ehrlich, "On Immunity with Special Reference to Cell Life," *Proc. Roy. Soc. London*, ser. B, *66* (1900), 424–448.

3. Karl Landsteiner, *Die Spezifizität der serologischen Reaktionen* (Berlin, 1933); rev. ed., *The Specificity of Serological Reactions* (Cambridge, Mass.: Harvard University Press, 1945).

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nutrition of the cells of body needed so many different side-chains. Jerome Alexander, Stuart Mudd, Felix Haurowitz, and others asserted instead that the specificity of the antibodies must be determined from outside, the antigen itself acting as a template for the formation of a complementary antibody structure.[4] From the mid-1930s, template (later called instructionist) theories dominated the understanding of antibody formation. The latest and at the time most advanced of these, that of Linus Pauling, postulated that normal, native, and as yet unspecific globulin molecules in the cell fold around antigen molecules, assuming appropriate tertiary structures that transform them into specific antibodies.[5]

In the early 1950s the template view was increasingly challenged. Stimulated by the notion of adaptive enzymes, Frank Macfarlane Burnet tried to solve one of the central problems of the template theories – namely, that of accounting for the continuous production of antibody long after the antigen had disappeared from the organism.[6] Burnet's revisionist attempt could not satisfy a widespread but unarticulated discontent with template theories among immunologists in the early 1950s, however. "I think most people knew that it didn't fit the facts. . . . Mark Adams and [Alwin] Pappenheimer and [Colin] McLeod and so on, all the people in the department . . . they knew the instruction theory isn't going to work," says an observer of the New York immunological scene in the early 1950s.[7]

The first to turn radically against the established template theories was Niels Kaj Jerne, then a senior scientific officer at the Danish State Serum Institute in Copenhagen.[8] In a paper published in the November 1955 issue of the *Proceedings of the National Academy of Sciences*, Jerne assumed instead that the blood plasma already possesses preformed antibody molecules with a

4. Silverstein, *History* (above, n. 1), chap. 4.

5. Linus Pauling, "A Theory of the Structure and Process of Formation of Antibodies," *J. Amer. Chem. Soc.*, *62* (1940), 2643–2657.

6. F. M. Burnet and F. Fenner, *The Production of Antibodies*, 2nd ed. (Melbourne: Macmillan, 1949); F. M. Burnet, *Enzyme, Antigen and Virus* (Cambridge: Cambridge University Press, 1956).

7. Interview with Gordon Lark, September 17, 1989.

8. The fact that Jerne was the originator of Darwinian and selective ideas in contemporary immunology has recently been obscured by a couple of reviewers of Gerald M. Edelman's recent book *Bright Air, Brilliant Fire* (New York: Basic Books, 1992): George Johnson ("Evolution between the Ears," *N.Y. Times Book Rev.*, April 19, 1992, pp. 2, 22) erroneously claims that Edelman won a Nobel Prize in 1972 "for establishing that the immune system works according to Darwinian principles," and Oliver Sacks ("Making up the Mind," *N.Y. Rev. Books*, April 8, 1993, p. 42) follows up on the rumor by making up a story of how Edelman's work should have led Burnet to the clonal selection theory.

certain degree of specificity against most foreign substances. He also postulated a stochastic mechanism for the generation of such antibody specificities and a mechanism of selection of the best fitting antibody. When an antigen enters the body, he said, there will always exist, by chance, a few preformed antibodies that happen to fit more or less well to the antigen; the antigen-antibody complex so formed will be engulfed by a phagocytic cell and transported to a system of cells capable of producing more antibodies of the same kind.[9] The strength of the selection theory, Jerne said, was its ability to explain several phenomena where template theories had failed. For example, it accounted for Burnet's problem, as well as for the booster phenomenon (the fact that the concentration of antibodies increases dramatically after a second injection of an antigen). It also made sense of the phenomenon of avidity – that is the fact that antibodies produced late in the course of immunization bind better to the antigen than early antibodies.[10]

The reactions to Jerne's *PNAS* paper varied. Some, for example Haurowitz, saw the theory as merely a revival of Ehrlich's old side-chain theory.[11] Pauling "understood and rejected the thing, probably within five seconds," says Jerne.[12] Most molecular biologists reacted against what they saw as a violation of the emerging central dogma in molecular biology. "It stinks," James D. Watson is said to have answered when Jerne presented the idea to him.[13] A few others responded in the affirmative, however: Günther Stent immediately became an ardent supporter,[14] and Joshua Lederberg told Jerne that he had "at least one second" for the proposal.[15] Even so, Jerne felt that the theory was not well received. "No others have come

9. Niels K. Jerne, "The Natural-Selection Theory of Antibody Formation," *Proc. Nat. Acad. Sci., 41* (1955), 849–857.

10. Jerne claimed that the theory also explained the existence of natural antibodies ("the presence in the blood of a large pool of normal globulins"), "the dominant part played by the surface of antigen particles in antibody induction," "the absence of auto-antibodies," "immunological paralysis and haptenic inhibition," and "the anamnestic reaction" (ibid., p. 856).

11. Felix Haurowitz, "Biosynthese der Proteine und ihre Beeinflussung durch Antigene," *Naturwisenschaften, 46* (1959), 60–63. See further below, section II.

12. Niels K. Jerne, "The Natural Selection Theory of Antibody Formation; Ten Years Later," in *Phage and the Origins of Molecular Biology*, ed. John Cairns, Günther S. Stent, and James D. Watson (Cold Spring Harbor. N.Y.: Cold Spring Harbor Laboratory of Quantitative Biology, 1966), p. 306 (hereafter cited as Jerne, "Ten Years Later").

13. Ibid.

14. Interviews with Günther Stent, November 1, 1988, and July 12, 1989 (see below, n. 43).

15. Joshua Lederberg to Jerne, December 28, 1955, Jerne Papers (see below, n. 42).

forth since I published these ideas," he replied to Lederberg, "but I am more content to have you than the whole clan of immunologists"[16] In fact, he maintains that a major cause for his decision in 1956 to leave experimental work and take up a science administration position at the World Health Organization (WHO) in Geneva was the apparent indifference to the theory.[17]

Jerne's theory was not forgotten, however. A year later, it was taken up and modified into a cellular selection theory. In a 1957 review article, David Talmage suggested that it was "tempting" to consider cellular selection instead.[18] Independently of Talmage, Burnet had also read Jerne's paper and was immediately intrigued by it, "pondering heavily on" why it was "so attractive, though obviously wrong."[19] By taking Jerne's Darwinian mechanism as the point of departure and replacing molecules with cell clones and their membrane receptors, "the whole picture fell into shape."[20] In a paper published in 1957, Burnet assumed that a large repertoire of lymphoid cell clones were precommitted to producing a similarly large repertoire of antibody specificities. When an antigen enters the body, a number of cell clones that happen to produce antibodies against that antigen are "selected" for and multiply into much larger clones of cells, producing antibody molecules specific against the intruding antigen.[21]

Burnet's clonal selection theory had the advantage that it did not violate the central dogma of molecular biology. Although it encountered some skepticism in the beginning,[22] the clonal selec-

16. Jerne to Joshua Lederberg, March 28, 1956.

17. Several interviews with Jerne. A few months after the publication of the *PNAS* paper Jerne accepted a position in WHO's Department of Biological Standardization in Geneve. He stayed there until 1962. Only after Macfarlane Burnet had directed attention to Jerne's paper, and after the subsequent triumph of Burnet's clonal version of the selection theory in the early 1960s, did Jerne go back to immunological research.

18. David Talmage, "Allergy and Immunology," *Ann. Rev. Med., 8* (1957), 247.

19. F. M. Burnet, *Changing Patterns: An Atypical Autobiography* (Melbourne: Heinemann, 1969), p. 204.

20. Ibid., p. 205.

21. F. M. Burnet, "A Modification of Jerne's Theory of Antibody Production Using the Concept of Clonal Selection," *Austr. J. Sci., 20* (1957), 67–68.

22. "[A]t times I felt a bit like Galileo confronting the Churth," says Burnet (F. M. Burnet, "The Impact on Ideas of Immunology," *Cold Spr. Harbor Symp. Quant. Biol., 32* [1967], 3). Gustav Nossal, then a graduate student of Burnet's, claims that "carrying the flag for clonal selection was a rather lonely battle for me!" (G. J. V. Nossal, "The Coming of Age of the Clonal Selection Theory," in *Immunology 1930–1980: Essays on the History of Immunology*, ed. Pauline Mazumdar [Toronto: Wall and Thompson, 1989], p. 42).

tion theory rapidly gathered a growing number of adherents, and within less than a decade the immunological community switched from believing in templates to believing in selection.[23] (The swift substitution of selection theories for instruction theories has been interpreted as an example of a paradigm shift in Kuhn's sense.[24]) The status of the theory was eventually settled at the Cold Spring Harbor Symposium on Antibodies in June 1967.[25] Since then, clonal selection has been the explicit theoretical foundation of immunology. So evident and ingrained has the theory become, that it has been referred to as a central dogma, analogous to that in molecular biology.[26] "We will not refer to it as the clonal selection theory (because a theory is something that is still being tested) but merely as Clonal Selection," says one standard textbook.[27]

Jerne's Autobiographical Discovery Account

The success of the selection theory never generated any priority disputes. Talmage immediately credited Jerne as the originator of the modern idea of selection in immunology.[28] Burnet even titled his 1957 paper "A Modification of Jerne's Theory . . . ," and he continued to credit Jerne: "As I hope I have always been careful to say, its 'onlie begetter' was Niels Jerne," he reiterated in his opening address to the Cold Spring Harbor Symposium.[29] By then

23. Gordon L. Ada and Gustav Nossal, "The Clonal-Selection Theory," *Sci. Amer.*, *257* (1987), 50–57.

24. Edward S. Golub, *Immunology: A Synthesis* (Sunderland, Mass.: Sinauer, 1987); Arthur M. Silverstein, "The Dynamics of Conceptual Change in Twentieth-Century Immunology," *Cell. Immunol.*, *132* (1991), 515–531.

25. Said Burnet, in his introductory remarks: "I think it is true to say that every paper I have read in a journal or listened to in a lecture room has been looked at critically . . . for its relevance to selective as against instructive theory" (Burnet, "Impact" [above, n. 22], p. 1).

26. Robert Olby, "Francis Crick, DNA, and the Central Dogma," *Daedalus*, *99* (1970), 938–987. The first to refer to the selection theory as a dogma were probably Gerald Edelman and Einar Gall, two years after the Cold Spring Harbor Symposium: "The unique aspects of the antibody problem are thrown into sharp relief by a body of facts . . . supporting the dogma that the immune response is selective" (G. M. Edelman and W. E. Gall, "The Antibody Problem," *Ann. Rev. Biochem.*, *38* [1969] 416).

27. Golub, *Immunology* (above, n. 24), p. 1.

28. Talmage, "Allergy and Immunology" (above, n. 18).

29. Burnet, "Impact" (above, n. 22), p. 2. Burnet also credited Talmage for simultaneously proposing a cellular selection theory (Burnet, "Modification" [above, n. 21] p. 67). The "onlie begetter" refers to the introductory dedication in William Shakespeare, *Sonnets* (London: Bell and Hyman, 1978): "To the onlie begetter of these insving sonnets Mr W. H."

Jerne had already established his reputation as a leading immunologist, partly as a result of the selection theory, but also as a result of his invention of the plaque technique, a simple method for detecting single antibody-producing cells.[30] When awarding him the Nobel Prize in 1984, the chairman of the Karolinska Institute Nobel committee cited the selection theory as the first of "his visionary theories [that] caused modern immunology to make major leaps of progress."[31] Thus, Jerne's 1955 paper stands out as a crucial event in the history of modern immunology at a time when the discipline was about to switch from a largely chemical and serological orientation to a more integrated biological approach: immunology "emerged as a subtle and sophisticated science out of the boredom of blind serology."[32]

So far, our understanding of the origin of the theory has been based on the first couple of paragraphs in an autobiographical essay, "The Natural Selection Theory of Antibody Formation; Ten Years Later," that Jerne wrote for the festschrift to Max Delbrück in 1966.[33] The story (henceforth "Ten Years Later") opens with an analogy between the selection theory and the Socratic view of learning as recollection:

> Can the truth (*the capability to synthesize an antibody*) be learned? If so, it must be assumed not to pre-exist; to be learned, it must be acquired. We are thus confronted with the difficulty to which Socrates calls attention in *Meno* (Socrates, 375 B.C.), namely that it makes as little sense to search for what one does not know as to search for what one knows; what one knows one cannot search for, since one knows it already, and what one does not know one cannot search for, since one does not even know what to search for. Socrates resolved this difficulty by postulating that learning is nothing but recollection. The truth (*the capability to synthesize an antibody*) cannot be brought in, but was already inherent. (p. 301)

Jerne then suggests that the Socratic theory of learning (in the

30. Niels K. Jerne and Albert Nordin, "Plaque Formation in Agar by Single Antibody-Producing Cells," *Science, 140* (1963), 405.

31. Hans Wigzell, "The Nobel Prize for Physiology or Medicine," in *Les Prix Nobel* (Stockholm: Almqvist and Wiksell International, 1985), p. 25.

32. B. Pernis and A. A. Augustin, review of *The Immune System: A Festschrift in Honor of Niels Kaj Jerne*, ed. C. Steinberg and I. Lefkovits, *Eur. J. Immunol., 12* (1982), 3.

33. Jerne, "Ten Years Later" (above, n. 12); page references will be given in parentheses.

Danish philosopher Søren Kierkegaard's version) is isomorphous with the selection theory:

> The above paragraph is a translation of the first lines of Søren Kierkegaard's "Philosophical Bits or a Bit of Philosophy" (Kierkegaard, 1844). By replacing the word "truth" by the italicized words, the statement can be made to present the logical basis of the selective theories of antibody formation. Or, in the parlance of Molecular Biology: synthetic potentialities cannot be imposed upon nucleic acid, but must pre-exist. (p. 301)

He also indicates that the Socratic-Kierkegaardian view may be one of the intellectual inspirations of the theory: "I do not know whether reverberations of Kierkegaard contributed to the idea of a selective mechanism of antibody formation that occurred to me one evening in March 1954,[34] as I was walking home in Copenhagen from the Danish State Serum Institute to Amaliegade" (p. 301). The construction of the theory was a momentary event: "The framework of the theory was complete before I had crossed Knippelsbridge. I decided to let it mature and to preserve it for a first discussion with Max Delbrück on our freighter trip to the U.S.A., planned for that summer" (pp. 301–302).

Second, Jerne logically reconstructs the reasoning leading to the theory:

> The train of thought went like this: the only property that all antigens share is that they can attach to the combining site of an appropriate antibody molecule; this attachment must, therefore, be a crucial step in the sequences of events by which the introduction of an antigen into an animal leads to antibody formation; a million structurally different antibody-combining sites would suffice to explain serological specificity; if all 10^{17} gamma-globulin molecules per ml of blood are antibodies, they must include a vast number of different combining sites, because otherwise normal serum would show a high titer against all usual antigens; three mechanisms must be assumed: (1) a random mechanism for ensuring the limited synthesis of antibody molecules possessing all possible combining sites, in the absence of antigen, (2) a purging mechanism for repressing the synthesis of such antibody molecules that happen to fit to autoantigens, and (3) a selective mechanism for promoting the synthesis of those antibody molecules that make the best fit to any antigen entering the animal. (p. 301)

34. The dating is evidently wrong; see below, n. 121.

Finally, Jerne elaborates on the local intellectual milieu at the Serum Institute in the early 1950s, particularly on the "succession of molecular biologists" who came to the laboratory, including Hans Noll, Günther Stent, and James D. Watson: "Over it all hovered the spirit of Max Delbrück who was shepherding his hand-picked band along the last stretch of the narrow path to the central fortress of biology. He made a few triumphant visits to Copenhagen, both before and after Lwoff assembled the court at Royaumont in 1952" (p. 302). Referring to the interaction between himself and the molecular biologists, Jerne hints at the intellectual inspiration for the theory:

> Meanwhile, in the same small laboratory room, I injected mixtures of diphtheria toxin and antitoxin into shaven rabbits, in order to study an esoteric property of antibodies that went under the name of "avidity." I admire the friendly stoicism with which the molecular biologists bore this incongruous activity. . . . Immunology was not then an "in" subject, and I had to apply antibodies to bacteriophage in order to hang on to the fringe. My avidity observations strengthened my faith in the truth of antibody selection. Antibodies produced by an animal against one antigen appeared to increase in "goodness of fit" during the course of immunization. This was true both for antitoxin and for anti-T4 antibodies. (pp. 302–303)

The phenomenon of avidity increase "had Darwinian overtones," says Jerne, concluding his account of the intellectual context of the selection theory (p. 303).

A Reconstruction of Jerne's Eureka Story

"Ten Years Later" belongs to the ranks of classical "eureka" discovery stories in the history-of-science literature. It has been used as a source material for a variety of purposes, including the reconstruction of the social origins of molecular biology, the construction of a general characterization of selection processes, a study of the nature-nurture debate, the reevaluation of self in modern immunology, and histories of immunology.[35] At least one philo-

35. See, e.g., N. C. Mullins, "The Development of a Scientific Specialty: The Phage Group and the Origins of Molecular Biology," *Minerva, 10* (1972), 51–82; L. Darden and J. A. Cain, "Selection Type Theories," *Phil. Sci., 56* (1989), 106–129; Harry Smit, *De biologie en methodologie van aanleg en omgeving* (Groningen: Wolters-Noordhoff, 1989), pp. 151 ff.; Alfred I. Tauber, *The Immune Self: Theory or Metaphor?* (Boston, Mass.: Cambridge University Press, forthcoming); A. M. Moulin, *Le dernier langage de la médicine: Histoire de l'immunologie de Pasteur au Sida* (Paris: Presses Universitaires de France, 1991), pp. 276 ff; Golub,

sophical reconstruction of the conceptual origin of the selection theory has been based on it.[36]

Jerne's autobiographical story is not satisfactory as a source document for the reconstruction of conceptual origins, however. A deliberate personal account, interspaced with anecdotes, mitigating between subtle irony and the nonpassionate description of experimental results, it fits better to the unwritten rules of the festschrift genre. It was probably never intended as a documentary of the events, and so, like most autobiographies, it "produces more questions than answers, more doubts by far . . . than certainties."[37] In fact, "Ten Years Later" reinforces a general impression among historians of science that retrospective discovery accounts are unreliable as evidence about the origin of scientific theories. Several authors have warned against the pitfalls of using these accounts,[38] supporting the opinion long held by literary scholars that autobiography is a fictional rather than factual genre.[39] It has also been suggested that the origin of theories cannot be adequately explained by reference to sudden insights. Several eureka stories turn out, on closer inspection, to be more complicated processes occurring over longer time periods.[40] Similarly, philosophers of

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Immunology (above, n. 24), pp. 9–10; Silverstein, *History* (above, n. 1); Debra Jan Bibel, *Milestones in Immunology: A Historical Exploration* (Madison, Wis.: Science Tech Publishers, 1988); and several essays in Mazumdar, *Immunology* (above, n. 22).

36. Kenneth F. Schaffner, "Discovery in the Biomedical Sciences: Logic or Irrational Intuition?" in *Scientific Discovery: Case Studies*, ed. T. Nickles, Boston Studies in the Philosophy of Science, vol. 60 (Dordrecht: Reidel, 1980), pp. 171–205; idem, *Discovery and Explanation in Biology and Medicine* (Chicago: University of Chicago Press, 1993).

37. James Olney, "Autobiography and the Cultural Moment: A Thematic, Historical, and Bibliographical Introduction," in *Autobiography: Essays Theoretical and Critical*, ed. James Olney (Princeton: Princeton University Press, 1980), p. 5.

38. Gerald L. Geison and James A. Secord, "Pasteur and the Process of Discovery: The Case of Optical Isomerism," *Isis, 79* (1988), 6–36; Ilana Löwy, "Variances in Meaning in Discovery Accounts: The Case of Contemporary Biology," *Hist. Stud. Phys. Biol. Sci., 21* (1990), 87–121.

39. Paul John Eakin, *Fictions in Autobiography: Studies in the Art of Self-Invention* (Princeton: Princeton University Press, 1985).

40. Frederic L. Holmes, "Patterns of Scientific Creativity," *Bull. Hist. Med., 60* (1986), 19–35. Good examples include Alan J. Rocke, "Hypothesis and Experiment in the Early Development of Kekulé's Benzene Theory," *Ann. Sci., 42* (1985), 355–381; Alfred I. Tauber and Leon Chernyak, *Metchnikoff and the Origins of Immunology: From Metaphor to Theory* (New York: Oxford University Press, 1991); and Craig Stillwell, "The Wisdom of Cells: The Integrity of Elie Metchnikoff's Ideas in Biology and Pathology," Ph. D. diss., University of Notre Dame, 1991.

science have argued that intuitive leaps could, at least partially, be analyzed into conceptual steps of a "logic of discovery."[41]

Such historical and philosophical corrections of classic discovery stories should make us more cautious when we approach Jerne's account of his moment of epiphany crossing the Knippelsbridge. In the course of my research for a biography of Niels K. Jerne, I have been generously given access to his collection of personal and scientific papers, laboratory protocols, notes, and manuscript drafts of his scientific papers, as well as the in- and outgoing correspondence.[42] These documents permit a finer-grained narrative reconstruction of the development of Jerne's experimental work and thinking. Over the past couple of years, I have also benefited from many hours of conversation with Jerne and his friends and colleagues;[43] some of these interviews have been followed up by correspondence over specific problems of interpretation.[44]

In the following sections I draw on this material to critically reconsider the origin of the selection theory. In section I, I use the methodology of textually fine-grained analysis to reconstruct the experimental background and the accumulation of anomalies to the template theories.[45] I follow Jerne's experimental career: his dissertation work on the avidity phenomenon in the late 1940s, his adoption in the early 1950s of bacteriophage as a tool for the study of antibody-antigen kinetics, and the finding in the summer of 1954 of an antibody in normal serum.

In section II, I discuss the crucial step in the generation of the new theory – namely, Jerne's interpretation of the finding of antibodies in normal serum in terms of the concept of natural antibodies, and the subsequent formulation of the selection theory to account for the experimental phenomena. Philosophical and

41. Norman R. Hanson, *Patterns of Discovery* (Cambridge: Cambridge University Press, 1958); idem, "An Anatomy of Discovery," *J. Phil.*, *64* (1967), 321–352; Schaffner, "Discovery" and *Discovery* (both above, n. 36).

42. Unless otherwise indicated, all unpublished material (including correspondence) quoted in this article is in the Jerne papers. The collection is now in the Manuscript Department, The Royal Library, Copenhagen, Denmark; it will be publicly accessible for research after the year 2000.

43. Most interviews were made by me. A few were made by Lotte Juul Nielsen (with Jerne in the spring of 1987, and with Günther Stent in 1988). With one exception (below, n. 73), all excerpts from interviews have been transcribed verbatim. Interviews in Danish are translated into English, but the Danish original is given in the notes.

44. In order to indicate points of agreement of conflicting interpretations I have included a number of Jerne's comments and gloss to a late version of the manuscript.

45. See Frederic L. Holmes, "Laboratory Notebooks: Can the Daily Record Illuminate the Broader Picture?" *Proc. Amer. Phil. Soc.*, *134* (1990), 349–366.

textual reconstruction alone cannot account for this step. Guided by the idea that the genesis of a scientific theory should also be understood against the personal and cultural context of the scientist,[46] I discuss the origin of the selection theory with reference to three sets of cultural contexts: Jerne's relations to the immunological tradition, including the heritage of Ehrlich and the dominant template theories; his biostatistical training and interests; and finally, the importance of the Darwinian ambience of the phage group.

I. THE SEROLOGICAL BACKGROUND AND THE AVIDITY PHENOMENON

Antibody Avidity as an Obstacle to Serum Standardization, 1943–1951

"I injected mixtures of diphtheria toxin and antitoxin into shaven rabbits, in order to study an esoteric property of antibodies that went under the name of 'avidity,' " Jerne wryly tells us in "Ten Years Later."[47] Later, however, he has downplayed the importance of the avidity work for the origin of the selection theory: "I do not think that this theory had really much to do with my experiments on antibody avidity."[48] Yet, as I will show, the avidity phenomenon did play an important role indeed: it was not just one of several routes to the theory, but the central problem during the first ten years of Jerne's scientific career, and a constant generator of new experiments that eventually led him to the notion of natural antibodies and the selection theory.

Born of Danish parents in London in 1911, Jerne grew up in the Netherlands, studied in Leiden for a couple of years, and moved to Denmark to be trained as a physician at the Medical School in Copenhagen.[49] In 1943, after having passed his preclinical examinations, he was employed as a part-time assistant in the small

46. See, e.g., Timothy Lenoir, "Essay Review: The Darwin Industry," *J. Hist. Biol.*, *20* (1987), 115–130. The idea has recently been stated most vigorously in Adrian Desmond and James Moore, *Darwin* (London: Michael Joseph, 1991). For a critique of the one-sided emphasis on the *social* context, see Thomas Söderqvist, "Existential Projects and Existential Choice in Science: Science Biography as an Edifying Genre," in *Telling Lives: Studies of Scientific Biography*, ed. Richard Yeo and Michael Shortland (Cambridge: Cambridge University Press, forthcoming).

47. Jerne, "Ten Years Later" (above, n. 12), p. 302.

48. Jerne to Kenneth Schaffner, March 28, 1978.

49. For biographical data on Jerne only standard biographical dictionary entries are available so far. The short biographical article by J. V. Spärck in *Dansk Biografisk Leksikon*, 3rd ed. (Copenhagen: Gyldendal, 1981) is the most detailed and most accurate.

Department of Standardization at the Serum Institute. The department had been set up in the 1920s by the League of Nations for the international standardization of biological substances and the biannual distribution of samples of standards to laboratories all over the world.[50] Being fluent in five languages, Jerne was supposed to take care of the department's correspondence, but since Denmark was occupied by the Nazis, his secretarial chores were limited. Instead, he was soon introduced to the daily practices in the laboratory, learning the basics of serological work and techniques for the standardization of toxins, toxoids, and antisera.

The standardization routines included measurements of the "strength" of unknown (e.g., antidiphtheria) serum preparations. The ability of an unknown serum to neutralize diphtheria toxin was compared with that of a serum of arbitrary, but internationally recognized standard, "strength." The method worked only for high antibody concentration levels, however (e.g., hyperimmune sera); at low antibody concentrations (e.g., in sera taken from the early phases of immunization), the neutralization curves deflected from parallelism, making comparisons impossible.[51] Jerne rapidly became fascinated by the difference between the effects of neutralization at high and low concentration levels – the "dilution effect," as he first called it. The effect was not an unknown phenomenon. Already in 1903, the German bacteriologist Rudolph Kraus had pointed out that "antitoxic sera possessed another characteristic [than concentration] which determined the rate of neutralization," and had coined the term "avidity" for this property.[52]

50. Thorvald Madsen, *Statens Seruminstitut: Institutets udvikling 1902–1940* (Copenhagen, 1940). The British Commonwealth had its own central laboratory in Hampstead.

51. The degree of neutralization was determined by means of a biological assay: samples of the reaction mixture were injected into the shaved dorsal skin of rabbits or guinea pigs, and the concentration of surplus toxin was measured in terms of the size of the necrotic skin areas. The size of the necrotic skin areas was plotted against the initial antitoxin concentration as a log dose/response curve, and the distance between the neutralization graphs of standard vs. unknown sera was then a measure of the relative "strength" of the unknown serum. This procedure was based on one essential assumption, viz., that the graphs were parallel lines. It was generally known, however, that the parallelity assumption was valid for high antibody concentration levels only; at low antibody concentrations the curves deflected from parallelism, making comparisons impossible.

52. Quoted from W. C. Boyd, *Fundamentals of Immunology* (New York, 1943), p. 189. The same opinion was expressed by Jerne's friend and mentor, the Danish mathematician Georg Rasch, whom Jerne quotes in the foreword to the dissertation: "the relative potency of an antitoxic serum must be measured by at least two constants" (Niels K. Jerne, *A Study of Avidity Based on Rabbit Skin Responses to Diphtheria Toxin-Antitoxin Mixtures* [Copenhagen: Munksgaard, 1951] p. 5).

Antibodies produced several months after an injection with antigen fit better (are more avid, greedy) than early antibodies. Although the consequences of the phenomenon for standardization procedures were first formulated in the early 1930s, these were not reflected in standardization routines.[53]

In 1944, while still a student, Jerne made some preliminary experiments on the "dilution effect." After having completed his medical degree in 1947, he began, now with Ole Maaløe as the new head of the department, experimental work for a dissertation on the kinetics of the diphtheria toxin-antitoxin system. He was not particularly interested in standardization as such, but, in accordance with a lifelong iconoclastic habit, he saw in this project a possibility of refuting the basic assumptions of the standardization procedures. If not only the quantity but also the quality of the antitoxin molecules is important, how then would it be possible to compare the potency of these two sera at all?

Another reason to take up the avidity study was the possibility of giving a physical-chemical explanation of the phenomenon. During his aborted student years in Leiden in the early 1930s Jerne had studied physics and chemistry, and he was leaning toward a physicochemical approach to biological phenomena. The fact that ten to twenty times as many antitoxic antibodies of low avidity were needed to neutralize toxin at low initial toxin concentrations was "suggestive of a dissociation mechanism":[54] "I said that one should talk about molecules, how strongly do these molecules bind to the toxin, a physical-chemical problem."[55] The idea was not new in serology, but so far it had not been pursued systematically.[56]

53. Cf. Jerne, *Study of Avidity*, particularly pp. 9–23. The routine attitude was rather "to hell with whether these curves are parallel or not" ("så giver vi fanden i om de er parallelle eller ej, de der kurver"; interview with Johannes Ipsen, March 17, 1988).

54. Jerne, *Study of Avidity*, p. 14.

55. "Jeg sagde at man skulle tale om molekyler, hvor stærk er disse molekylers bindning til toxinet, et fysisk-kemisk problem" (interview with Jerne, May 5, 1987).

56. Around the turn of the century, the Swedish chemist Svante Arrhenius had observed that the neutralization curve was similar to a typical equilibrium curve "between a body in partial dissociation and its products of dissociation" (quoted in Jerne, *Study of Avidity* [above, n. 52], p. 5). Attempts had also been made to apply this thinking in standardization – for example, by Glenny, who claimed that avidity was due to different "firmness of union" between toxin and antitoxin (Boyd, *Fundamentals of Immunology* [above, n. 52], p. 189), and by others who also hinted at a molecular explanation: "Sera that dissociate readily, are slow to combine and have flat neutralization curves are frequently spoken of as 'non-avid' " (quoted in Jerne, *Study of Avidity*, p. 16). " 'Flat' here is laboratory slang for curves (log dose/response) that don't reach full neutralization" (Jerne, pers. comm.).

During the following four years Jerne performed a long series of neutralization experiments with high-avid and low-avid sera under different experimental conditions. Simultaneously, he worked out a physical-chemical model for the neutralization process based on assumptions of chemical equilibria. It turned out that calculations based on a mutual multivalency of toxin and antitoxin permitted a reasonable explanation of the experimental data if appropriate values were chosen for the association constant: high values of the association constant could account for neutralization curves with high-avid sera, and low values accounted for curves with low-avid sera.

This was enough to pass a dissertation defense; it was also a qualified contribution to the theoretical understanding of the antigen-antibody reaction and a contribution to a broader movement to apply physicochemical reasoning to serological phenomena, as witnessed by the fact that the dissertation was later frequently cited as a standard reference on avidity.[57] But Jerne extended the experimental program to studies of the change in avidity in the course of immunization and could easily demonstrate a general increase in avidity from early sera to late sera in a number of mammal species. A change in avidity, then, could be understood simply in terms of a shift in the association constant for the antigen-antibody reaction.[58]

Although Jerne did not embark on a reasoned discussion of the possible mechanism for the avidity increase in terms of theories of antibody formation in the dissertation, the study nevertheless contains a passage that, in hindsight, bears a certain similarity to the selection theory proposed a couple of years later: "It is conceivable," he wrote, "that, *before* the antigen stimulus is applied, the specific cells are engaged in the production of unspecific globulin, and start the production of antitoxin immediately the antigen molecules have penetrated them."[59] In another passage he referred to the work of Lewis B. Holt, who had suggested that

57. "It is known [from Jerne] that the avidity of antibody increases with duration of immunization," wrote B. Pernis, M. W. Cohen, and G. J. Thorbecke, "Specificity of Reaction to Antigenic Stimulation in Lymph Nodes of Immature Rabbits," *J. Immunol., 91* (1963), 541–552, quotation on p. 551. See also J. W. Uhr., "The Heterogeneity of the Immune Response," *Science, 145* (1964), 457–464.

58. "Producing first an antitoxin of almost infinitely low avidity ($K_1 = 0$) which would not be able to neutralise any toxin at all and thus would be indistinguishable from unspecific globulin, the avidity of the antitoxin molecules turned out steadily increases. After say, 3 weeks the avidity constant many be about $K_1 = 0{,}02$, and it may reach a value of $K_1 > 1$ when sufficient time has elapsed" (Jerne, *Study of Avidity* [above, n. 52], p. 135).

59. Ibid., p. 135 (my emphasis).

the antibodies produced in the secondary response were "already present in the animal as reserve or stored antibody."[60] This reference is interesting because, even though Holt referred only to the secondary response, it could nevertheless be interpreted as that of preformed, "natural" antibodies – in fact, Jerne quoted Holt's results as the release of "stored *preformed* antibody."[61] By substituting "specific globulin" for "unspecific globulin" in the first passage, Jerne could have formulated the selection theory already in 1951.

The cited passages cannot be unambiguously interpreted as precursors to the selection theory, however. *A Study of Avidity* was not a treatise on antibody formation. When the faculty opponent reacted against Jerne's antitemplate theoretical hints ("but not by already formed antitoxin molecules, however. Is that clearly formulated?"),[62] Jerne did not argue with him. Whether he was agreeing or merely biding his time, we do not know. For the time being, he seems to have been more occupied with the physicochemical approach to antigen-antibody kinetics, and with the critical consequences of the work for the assumptions of serum standardization in general.[63] As he wrote, ironically, in the internal magazine of the Serum Institute: "Standardization has one large practical value, however, which is probably best expressed by the words of the poet: 'to give to airy nothing a local habitation and a name.' "[64]

Getting the Attention of the Molecular Biologists: Experiments on Phage-Antiphage Kinetics, 1950–1952

Jerne sent his dissertation to a number of leading immunologists, but he did not consider himself an immunologist. "I only went to meetings at the Serum Institute," he says, "I didn't go to inter-

60. L. B. Holt, "Quantitative Studies on Diphtheria Prophylaxis: The Second Response," *Brit. J. Exp. Pathol.*, *31* (1950), 240.

61. Jerne, *Study of Avidity* (above, n. 52), p. 139 (my emphasis).

62. "[M]en dog ikke af allerede dannede antitoxin molekyler. Er det klart formuleret?" (Jerne papers, box 1951).

63. See also Niels K. Jerne and Ole Maaløe, "Standardization of Diphtheria Toxoid: Some Theoretical and Practical Considerations," *Bull. W. H. O.*, *2* (1949), 49–57; Ole Maaløe and Niels K. Jerne, "The Standardization of Immunological Substances," *Ann. Rev. Microbiol.*, *6* 1952), 349–366.

64. "Dog har Standardiseringen en stor praktisk værdi, der maaske udtrykkes bedst ved digterens ord: 'to give to airy nothing a local habitation and a name' " (*Mikro* [State Serum Institute internal magazine], no. 5 [August 1949], 49). The poet was, of course, William Shakespeare (*A Midsummer Night's Dream*, act 5, scene 1, line 12): "And as imagination bodies forth / The forms of things unknown, the poet's pen / Turns them to shapes, and gives to airy nothing / A local habitation and a name."

national immunology meetings . . . [they] were completely uninteresting . . . because they dealt with things such as allergy, etc."[65] His main professional relations were with the international circle of standardization experts, and with a diverse and somewhat diffuse community of people interested in statistics and biometrics (see below). In the early 1950s, however, he began to orient himself toward a new scientific peer group – the burgeoning molecular biologists. This reorientation turned out to be decisive for his further scientific career.

Jerne was conducting a few additional control experiments for the dissertation and laying plans for starting a biometrical discussion club in Copenhagen when Günther Stent and James D. Watson arrived in the laboratory to spend the year 1950–1951 as postdoctoral investigators.[66] Stent recalls his first encounter with Jerne as "sort of surrealistic": "We were there in the lab, and all in a sudden a man walks in, behind him a technician, and they were carrying a board on which a rabbit was stretched out. . . . I thought it was horrible to torture animals like this . . . like Christ they were crucified on the board."[67] The crucified rabbits were those used by Jerne for the biological assay of diphtheria toxin. But except for its surreal qualities, the two Americans considered Jerne's avidity work boring.[68] In their view, antibodies were just a tool for studies of phage. "They wanted to find the gene," Jerne says; "I mean, I didn't have a great auditorium. Here you are, antibody this, antibody that, and so what the hell. They weren't really much interested."[69]

Instead, bacteriophage and phage genetics were the daily discussion topics in the laboratory. As Jerne says in "Ten Years Later," immunology was not an "in" subject, and he started to work with bacteriophage in order to "hang on to the fringe."[70] While

65. "Jeg var kun med til møder på Seruminstitutet. Jeg var ikke med til internationale immunologimøder. . . . De immunologiske møder var fuldstændig uinteressante, i mine øjne var de uinteressante for det handlede om sådan noget som allergi osv" (interview with Jerne, May 5, 1987).

66. For details, see James D. Watson, *The Double Helix: A Personal Account of the Discovery of the Structure of DNA* (London: Weidenfeld and Nicolson, 1968); Günther Stent, "The Copenhagen Spirit," in *The Molecular Biology of Bacterial Growth*, ed. Moselio Schaechter et al. (Boston: Jones and Bartlett, 1985), pp. 377–384; Ole Maaløe, "How It All Began," in *The Immune System: A Festschrift in Honor of Niels Kaj Jerne*, ed. C. Steinberg and I. Lefkovits (Basel: Karger, 1981), I, 1–5.

67. Interview with Günther Stent, July 12, 1989.

68. Ibid.

69. Interview with Jerne, February 10, 1988.

70. Jerne, "Ten Years Later" (above, n. 12), p. 302.

finishing the manuscript for the dissertation in the winter of 1951, he learned the basics of bacteriophage theory, and he soon began to do experiments on his own. It was generally known among phage researchers that the inactivation (neutralization) of phage by antiserum proceeds exponentially according to the function $\log s = -kt/d$, where s = logarithm of the fraction of surviving phage particles, t = time, and d = dilution of antiserum. A good antiphage serum could have a k-value of 500–1000/minute. The validity of the widely used phage plaque assay (see below) rested on the assumption that the phage-antiphage reaction was irreversible;[71] otherwise, if inactivated phage particles could dissociate from the antibody and regain their infectivity (e.g., during incubation on the petridish), the assay would be worthless. The irreversibility assumption was valid for all practical purposes, since phage serology utilized late sera from hyperimmune animals. But since Jerne had been convinced through his dissertation work that the diphtheria toxin-antitoxin reaction was *reversible* for low-avid sera, he thought that this must be true for the phage-antiphage system as well. In retrospect, he believes that this suspicion motivated him to go into bacteriophage work: "I then decided to switch my attention to the inactivation of bacteriophage by antiphage serum. . . . I doubted their experimental methods, and doubted their conclusion of irreversibility."[72]

Stent has a less rational story to tell. He thinks that Jerne got the impulse to start with phage one day when watching the two Americans work with antiphage sera at the opposite bench. The normal procedure among phage researchers was to do all experiments in standard bacterial growth medium, that is, nutrient broth (bouillon). Stent recalls the following exchange: *Jerne*: "Why do you neutralize in bouillon?" *Stent*: "Well, everybody does it." *Jerne*: "It's crazy, you should do the neutralization in a well-defined medium, a buffer or so." *Stent*: "Get lost!"[73] Stent also recalls that Jerne was offended: "I think then he was mad or something, furious that we told him to go away," and his lasting impression is that Jerne did his first phage-antiphage neutralization experiments mainly "to show that here were two . . . jerks who don't

71. Hershey's assumption that "the phage-antiphage reaction must be considered irreversible" was taken for granted; see A. D. Hershey, "Experiments with Bacteriophages Supporting the Lattice-Hypothesis," *J. Immunol.*, *47* (1943), 77–87; quotation on p. 85.

72. Jerne to Ed Goldberg and [?] Karam, February 22–23, 1992.

73. This is not a verbatim transcript, but a dramatized version of an excerpt of an interview with Günther Stent, November 1, 1988.

know anything about immunology, that they don't use proper procedure."[74]

Whatever the motivation, however, Jerne started to inactivate phage in well-defined media. He found that the rate of T4 inactivation was highly dependent on the salt concentration of the reaction medium – inactivation was in fact a 1000 times faster in 0.001 N NaCl than in 1 N NaCl, giving *k*-values of 100,000/minute or more.[75] He tried different compositions of the medium, "and finally for some crazy reason, he did it in distilled water."[76] The result was astounding: in distilled water, inactivation turned out to be totally inhibited.[77] And when small amounts of normal serum or peptone were added, the phage particles were again inactivated – now at an extremely high rate. The obvious explanation was that a factor in normal serum was needed in order for the reaction between phage and antiphage to take place. Both effects were new and unexpected. Encouraged by Delbrück to publish the results "to avoid priority problems,"[78] Jerne sent a short communication to *Nature*.[79]

In September 1951 the small ad hoc phage group in Copenhagen collapsed. Stent left for Paris, Watson for Cambridge, and Maaløe took off for a sabbatical with Delbrück at Caltech. Jerne was left alone to take care of the standardization routines and the preparations for the annual WHO standardization meeting in Geneva. He would probably not have been able to continue his phage work had not a graduate student in biochemistry, Lis Skovsted, unexpectedly arrived in October. Drawing on her biochemical experience, Jerne started a series of experiments on the cofactor phenomenon and spent most of the late autumn of 1951 trying to identify the serum factor. "I have been possessed by 'third factor'

74. Interviews with Günther Stent, November 1, 1988, and July 12, 1989.

75. Jerne to Ed Goldberg and [?] Karam, Februrary 22–23, 1992.

76. Interview with Günther Stent, November 1, 1988. Maaløe's technician remembers the occasion when they were having lunch around the table in the laboratory and were talking about "what kind of reagents one usually uses, and then he [i.e., Jerne] says: why hasn't anybody tried plain water . . . so everybody smiled, I mean plain water, it was almost sort of stupid to imagine" (interview with Jens Ole Rostock, March 22, 1988).

77. "I then made a strange finding," Jerne says, "namely that inactivation of T4 did not occur when the medium was *distilled water*!" (Jerne to Ed Goldberg and [?] Karam, February 22–23, 1992).

78. Max Delbrück to Jerne, August 13, 1951.

79. Niels K. Jerne, "Bacteriophage Inactivation by Antiphage Serum Diluted in Distilled Water," *Nature*, *169* (1952), 117–118. The editors were evidently not as impressed as Delbrück had been, since the paper was published only five months later.

and worked on it without interruption," he told Maaløe.[80] None of the daily trials of fractionation, extraction, or dialysis shed much light on the nature of the serum factor, however, so in early January 1952 Jerne changed the research strategy: instead of trying to isolate a serum component, small amounts of various prospective factors were added. It turned out that lysozyme displayed activity down to the 0.1 ppm level, sometimes even at the 0.01 ppm level. Jerne concluded that lysozyme "may substitute for a serum component necessary for the inactivation of bacteriophage."[81] Again the phage people were astonished: "Your recent letter was most exciting – a real incredible discovery!! – In a way the most Moewus like fact yet discovered in phage," Watson wrote back from Cambridge.[82]

The first enthusiasm was soon followed by doubts. The effect of lysozyme turned out to be unspecific: other substances with high isoelectric points (such as protamin), and basic amino acids (such as arginine and lysine), gave the same effect. Furthermore, the results were not reproducible in the lower concentration rage, and Jerne became somewhat disillusioned. "I have lost some of my enthusiasm," he complained.[83] The lack of reproducibility in the low concentration range continued to haunt him throughout most of the spring of 1952. In May he tried "dump experiments,"[84] and it turned out that the size of the vessel rather than the dump itself was the decisive factor: "I have now erected the hypothesis," he said, "that the glass wall takes up antibody molecules from distilled water and that third-factor substances can substitute for them on the glass wall and bring them back into the fluid. Large vessel → smaller glass wall per volume," and he speculated that the factor

80. "Jeg har været besat af 'tredie factor' og arbejdet med den uafbrudt" (Jerne to Ole Maaløe, January 18, 1952, Maaløe papers, in the custody of Aase Maaløe, Copenhagen).

81. MS of lecture at the Carlsberg Laboratory, March 1952 (Jerne papers, box 1952).

82. James D. Watson to Jerne, February 13, 1952. Watson refers to the German microbial geneticist Franz Moewus, whose data were considered by a number of life scientists to be unreliable and the experiments irreproducible; see Jan Sapp, *Where the Truth Lies: Franz Moewus and the Origins of Molecular Biology* (Cambridge: Cambridge University Press, 1990).

83. "[J]eg har tabt noget af begejstringen" (Jerne to Ole Maaløe, undated [probably March 1952], Maaløe papers).

84. The dump experiments were probably adopted from Anderson, who had devised a "dump experiment" to decide whether the tryptophane cofactor interacts with the phage to make it "active" or with the bacterium to make it "sensitive"; see E. Wollman and G. Stent, "Studies on Activation of T4 Bacteriophage by Cofactor. I. The Degree of Activity," *Biochim. Biophys. Acta*, *6* (1950), 293–306.

was needed to help the interaction between antigen and antibody in the neutral environment of distilled water.[85]

Jerne presented the results of the third-factor experiments at the first international phage colloquium in Royaumont in July 1952. The paper was somewhat marginal in this forum, which gathered "everyone who counted for anything in the world of phage,"[86] and where Alfred Hershey and Martha Chase presented their famous blender experiment that confirmed that genes are made of DNA.[87] Jerne's paper was not overlooked – Delbrück mentioned it separately in his report from the meeting under the heading "The Jerne Effect"[88] – but in spite of the attention and the encouraging attitudes shown by the molecular biologists at Royaumont, Jerne's interest in the salt and cofactor effects soon faded. On his return to Copenhagen he made a few extra experiments to discard André Lwoff's suggestion that the effect of protamine might be due to its chelating properties, and he finished the manuscript by the end of September 1952.[89] He conducted only a few experiments during the autumn of 1962 and the winter of 1953, and although he had infrequent discussions about the importance of the glass wall,[90] this was the end of eighteen months' research on the effects of ionic strength and cofactor on antibody-antigen kinetics.

Using Bacteriophage as a Tool in Immunology: The Reactivation of the Phage-Antiphage Reaction, 1952–1954

The two papers on the salt and cofactor effects received relatively little attention in the literature, in spite of Delbrück's

85. "Jeg har nu opstillet den hypotese, at glasvæggen optager antistofmolekylerne fra det detstil. vand og at de 3-faktor stoffer kan erstatte dem paa glasvæggen og føre dem tilbage i vædsken. Større kolbe → mindre glasvæg pr. volumen" (Jerne to Ole Maaløe, June 4, 1954, Maaløe papers).

86. François Jacob, *The Statue Within* (New York: Basic Books, 1988), p. 265.

87. A. D. Hershey and M. Chase, "Independent Functions of Viral Protein and Nucleic Acid in Growth of Bacteriophage," *J. Gen. Physiol., 36* (1952), 39.

88. M. Delbrück, "International Phage Symposium, Abbaye Royamont, July 26–August 1, 1952," mimeographed report to National Foundation for Infantile Paralysis, 1952 (Jerne papers, box 1952).

89. N. Jerne and L. Skovsted, "The Rate of Inactivation of Bacteriophage T4r in Specific Anti-Serum," *Ann. Inst. Pasteur, 84* (1953), 73–89.

90. E.g., during a short visit to Lwoff, Siminovich, Monod, Grabar, and others at Institut Pasteur in October 1952, Jerne discussed different ways of systematically investigating the glass wall effect, and during a visit to John Humphrey at the National Institute for Medical Research, London, half a year later he discussed future experiments with different salt concentrations and different ions (Jerne papers, box 1952).

prophecy that "several of us will be using this discovery."[91] Today Jerne maintains that "it wasn't anything that had any importance."[92] Seen in hindsight, his phage work in 1951–1952 was indeed a blind alley, a seemingly unnecessary sidetrack in the hunt for an understanding of the avidity phenomenon. More important than the scientific results per se, however, was the fact that the work opened the door the world of early molecular biology. Through his work on the cofactor Jerne established himself as a gifted member of the phage community.

Unlike the phage people, however, Jerne was not interested in using antibody as a tool in bacteriophage studies: in a talk at the Carlsberg laboratory in the spring of 1952, he stressed his wish to reverse the priorities, and to utilize bacteriophage as a tool in studies of early, low-avid antibodies instead.[93] The experiences with phage had provided him with a new instrument for studying the kinetics of the antigen-antibody reaction. Jerne realized, probably right from the beginning, that the increased sensitivity of the phage-antiphage system could help him to go deeper into the avidity problem. He became "very impressed with the accuracy with which he could measure titres with phage by the inactivation curve."[94] The limited sensitivity of the diphtheria toxin assay (it could only measure toxin concentrations above 10^9 molecules/ml) had prevented him from demonstrating experimentally the reversibility of the diphtheria-antidiphtheria toxin reaction. The phage-antiphage system had no such limitations: "I am at present engaged in work with bacteriophage-antiphage interaction where the great advantage consists in sensitivity," he wrote to a fellow serologist in the spring of 1952; "every single virus particle that is not inactivated can be made to show up."[95] This was

91. Max Delbrück to Jerne, August 13, 1951. The *Nature* paper has been cited nine times and the *Annales de l'Institut Pasteur* paper thirty-four times between 1955 and 1974, mainly for the finding that ionic strength has an effect on virus-antivirus kinetics. Two biophysicists, John R. Cann and Eugene W. Clark, later confirmed Jerne's findings and tried to explain them as being caused by "electrostatic interaction between oppositely charged, specific antibody and antigen combining sites rather than by interaction between the net charges carried by the two particles" ("Kinetics of the Antigen-Antibody Reaction," *J. Amer. Chem. Soc.*, *78* [1956], 3630–3631).

92. "Men det var jo ikke noget der fik nogen betydning" (interview with Jerne, April 29, 1987).

93. Jerne paper, box 1952.

94. Interview with Günther Stent, November 1, 1988.

95. Jerne to Mollie Barr, April 1, 1952.

"immunologically a unique experiment," he characterized it a couple of years later.[96]

During the salt and cofactor experiments Jerne had looked for sign of reversibility of the phage-antiphage complex, without being able to demonstrate it.[97] In May 1952 he began to immunize a horse with T4 bacteriophage to produce both an early (8 days), low-avid, and a late (120 days), high-avid antiphage serum. He was evidently in doubt about how to apply the new experimental system to demonstrate reversibility, however, because when WHO offered him a temporary appointment to make an inspection journey to standardization laboratories in Southeast Asia, he gladly accepted. The WHO assignment lasted through the spring and summer of 1953. The lecture manuscripts from the journey disclose that Jerne's thoughts were still lingering on the avidity problem and the use of the phage system.[98] After returning from Asia in early September 1953, he apparently still had uncertainties about how to proceed. He made a few attempts to monitor early immunization in vivo: by injecting a rabbit with a large dose of T4, and measuring the rate of disappearance of phage in the blood, he could measure the rise of antiphage activity in the serum, and he found signs of immunity as early as twenty-four hours after injection. The results were not conclusive, however, and he never published anything from these experiments, his only in vivo studies ever.[99] "I don't foresee any interesting developments," he wrote to Delbrück.[100]

His colleagues recall him as being in a waiting position during most of the autumn of 1953. Gordon Lark, a new postdoctoral fellow in the laboratory, remembers that "[Jerne] would come in and say: 'Aha, we should be doing something, I suppose . . . I suppose I should do something, maybe an experiment or something, but, you know, what should I do?' And [he] didn't do anything for a while and he would come in every day."[101] Perla Avegno, an Italian microbiologist who arrived in January 1954 to spend six months as a postdoctoral fellow, recalls that Jerne was unwilling

96. Niels K. Jerne and Perla Avegno, "The Development of the Phage-Inactivating Properties of Serum during the Course of Specific Immunization of an Animal: Reversible and Irreversible Inactivation," *J. Immunol.*, *76* (1956), 201.

97. Jerne and Skovsted, "Rate of Inactivation" (above, n 89), p. 73. He found one single early case in the literature reporting reactivation of inactivated phage particles by dilution of phage-serum mixtures: C. H. Andrewes and W. J. Elford, "Observations on Anti-Phage Sera. I: 'The Percentage Law,' " *Brit. J. Exp. Pathol.*, *14* (1933), 367–383.

98. Jerne papers, box 1953.

99. Jerne papers, box 1953.

100. Jerne to Max Delbrück, December 18, 1953.

101. Interview with Gordon Lark, September 17, 1989.

to do experimental work and that he was "in a sort of 'contemplative' state from which he did not wish to be disturbed."[102]

In mid-January 1954, however, Jerne returned "reluctantly to antiphage serum and phaque-counting" and started a series of highly focused experiments with the early and late anti-T4 sera that he had produced in May 1952.[103] He engaged Avegno as his bench coworker, and they began by demonstrating that a phage–late-antiphage complex could be dissociated by heating. Reactivation at 65° was small (5–10 percent) compared to the total number of inactivated phage particles, and the result could have been due to the disintegration of phage clumps, but Jerne nevertheless interpreted it as a proof of the reversibility of phage inactivation – a somewhat worrying result for the phage workers. The next step was to see if the reversibility of the phage-antiphage complex upon heating "might show up better when using *early* serum."[104] When undiluted early serum was mixed with phage he obtained inactivation curves that indicated that considerable reactivation took place when samples were heated at 65 °C for five minutes before plating. This was "a little disturbing": "[W]hat sort of 'survivors' are we counting on the plates if reactivation comes so easily?" he wrote to Stent; it is true that reactivation did not take place at 37°, but evidently it did at 65 °C, so "perhaps things happen in the 45° agar or on the plates."[105]

How could the kinetics of reactivation of these early sera be followed in a systematic way? In order to illuminate the reactivated phages Jerne modified the standard plaque assay. It was usually performed in four steps: (1) at time t_0 phage and antiphage serum were mixed in a reaction tube, and inactivation of the phage started immediately; (2) at different times (t_1, t_2, . . . , t_n) small samples from the reaction tube were diluted 1/100 or more in order to stop the inactivation; (3) a sample from the dilution was mixed with bacteria and soft agar and plated on hard agar in a petri dish; (4) after incubation overnight, each surviving phage particle and its progeny had infected and lysed bacteria in their immediate surroundings, giving rise to a clear circular spot (plaque) on the dish. The number of plaques corresponded to the number of surviving phage particles in the reaction tube.

102. Perla Avegno to Söderqvist, June 14, 1990, and telephone interview with Avegno, June 20, 1990.

103. Jerne to Günther Stent, April 10, 1954, Stent papers, in the custody of Günther Stent, Berkeley.

104. Ibid.

105. Ibid.

The standard procedure could not distinguish between noninactivated phages and reactivated phages. As Jerne said to Delbrück: "By just looking on plates for survivors you see nothing of these events – just as a picture of the Red Sea won't show you the Jews that got over nor the Egyptians that were drowned."[106] So, instead of directly plating the reaction samples in step 2, Jerne introduced two extra steps into the procedure: (2a) the sample from the dilution (step 2) was mixed with bacteria in a "decision tube" in which any particle that had attached to an antibody molecule, but had not yet been inactivated, would have the chance to infect a bacterium; (2b) after 10 minutes (i.e., before a new generation of phage particles had formed), a concentrated, high-avid serum was added to the decision tube, thereby killing all phage particles that had not, by adsorbing to a bacterium, produced an infective center that could not be inactivated by serum. Five minutes after adding the killing serum the contents of the "decision tube" were poured onto a plating dish, and each infective center would produce a plaque.[107]

The effect of using this method of indirect plating was dramatic. The efficiency of the indirect procedure was almost as high as that of the normal direct plating method, so the only possible interpretation was that the higher number of surviving phage particles obtained by direct plating was due to reactivation. "These are, as you will see," Jerne told Stent, "very solid effects; and excellently reproducible."[108] (When he repeated the indirect plating procedure with the late serum (without heating), Jerne could not demonstrate any reactivation.) Hence, the phage group's assumption that the phage-antiphage reaction is irreversible was invalid for low-avid sera. Given Jerne's earlier theoretical interpretation in his dissertation, these results were hardly surprising; however, now the reversibility of the complex between antibodies and antigen had been demonstrated experimentally with a system that was much more sensitive than the rabbit-skin system.

106. Jerne to Max Delbrück, May 8, 1954. The expression is a paraphrase of Kierkegaard's introductory aphorisms (Diapsalmata) to *Either/Or*: "My life achievement amounts to nothing at all, a mood, a single color. My achievement resembles the painting by that artist who was supposed to paint the Israelites' crossing of the Red Sea and to that end painted the entire wall red and explained that the Israelites had walked across and that the Egyptians were drowned" (Søren Kierkegaard, *Either/Or*, trans. H. V. Hong and E. H. Hong [Princeton: Princeton University Press, 1987], I, 28).

107. Jerne papers, box 1954; Jerne and Avegno, "Phage-Inactivating Properties" (above, n. 96).

108. Jerne to Günther Stent, April 10, 1954, Stent papers.

The indirect plating technique opened the way for detailed quantitative studies of the reaction kinetics of early, low-avid sera and of the influence of different parameters on the reaction kinetics. For the rest of the spring and early summer of 1954 Jerne and Avegno performed almost daily experiments under varying experimental conditions to determine the reaction rate constants and their dependence on the salt concentration. Jerne presented the results at the phage meeting in Göttingen in mid-June 1954; the full paper was not submitted for publication until a year later.[109]

The research on the avidity phenomenon in the late 1940s had provided a strong impetus for Jerne to adopt the methodology of the phage group and use bacteriophage inactivation as a new and more sensitive tool for avidity studies. By means of the T4–anti-T4 experimental system he had now demonstrated the reactivation of the antibody-antigen reaction, and thereby the experimental program that he had started in the mid-1940s came to an end.

The P-star Phenomenon and the Discovery of a Specific Antibody in Normal Serum, February–June 1954

Jerne's immunological work as a whole might have come to an end too, had the experiments not taken an unexpected turn. In the course of the experimental series discussed above, Jerne stumbled upon a new phenomenon that led him to the observation of antibodies in normal serum. This observation, in turn, opened up a new venue of research for him, and came to be one of the crucial factors in the subsequent formulation of the selection theory.

The new experiments were made possible only with the highly sensitive bacteriophage system that Jerne had developed in the course of his work on avidity. So far, he had made all his phage experiments with a T4 strain ($T4r^+$, or T4.38) that requires the presence of the amino acid tryptophan in order to infect *Escherichia coli*.[110] All solutions and growth media had to be prepared with small amounts of tryptophan added to them. When trying out the

109. Phage Information Service no. 7, Phage Meeting, Göttingen, June 18–19, 1954 (mimeo), Jerne papers, box 1954; Jerne and Avegno, "Phage-Inactivating Properties" (above, n. 96).

110. Tom Anderson had discovered in 1945 that certain strains of the T-even phages could not adsorb to *E. coli* unless they were activated by L-tryptophane: T. Anderson, "The Role of Tryptophane in the Adsorption of Two Bacterial Viruses on Their Host, *E. coli*," *J. Cell. Compar. Physiol.*, *25* (1945), 17–26. L-tryptophane action was later found to be reversible: T. Anderson, "The Activation of the Bacterial Virus T4 by L-tryptophan," *J. Bacter.*, *55* (1948), 637–649.

indirect plating method in late February 1954, Jerne also plated some control samples via bacteria (of the *E. coli* B/1 strain) that had been washed in physiological saline to exclude tryptophane. Without tryptophan in the decision tube, the phage particles remained inactive and could not infect the bacterium; hence these samples constituted a control. On one occasion, however, he observed that if the phage particles were treated with early serum before being used for control, they could indeed infect the bacteria in the decision tube even without the presence of tryptophane: "if the washed fresh bacterial B/1 culture is resuspended in saline (no tryptophane) free phage controls can no longer adsorb, but 'inactivated' T4 can!"[111]

The result was quite unexpected. There was no appreciable amount of tryptophane in early serum, so evidently normal, early serum contained some factor that could confer infective activity upon the phage and hence replace the action of tryptophane. A few days later Delbrück came on one of his irregular Copenhagen visits, and Jerne informed him about the recent findings. Delbrück seems to have been unimpressed, however. Jerne reported that Delbrück "thought it a big mess" and considered his earlier work on the salt and cofactor effects to be more interesting. "This disencouraged me a little," Jerne confessed, and he asked Stent for advice: "I can't help finding that the above story may have some consequences and I should be very glad to have your opinion – not least because you are the tryptophane expert – before I throw it all in a corner. Serum is and always was a big mess, and I sometimes wish I never were mixed up into it."[112]

He continued to get "mixed up," however. During the late spring of 1954, and simultaneously with the phage-antiphage reactivation experiments, Jerne made a series of experiments on his own to elucidate the kinetics of the formation of the serum-activated phage particles – P-stars (or P*), as he called them. For example, he found a pronounced initial lag: P-star formation followed a multiple hit curve, indicating that four or five factor molecules were needed. At the phage meeting in Göttingen in mid-June, he spent the second half of his talk discussing the production of P-stars and the kinetics of their formation. "I clearly remember the actual lecture [in Göttingen]," he says, "because I felt so happy that Delbrück was much impressed."[113]

What kind of a serum factor was involved in P-star formation?

111. Jerne to Günther Stent, April 10, 1954, Stent papers.
112. Ibid.
113. Jerne to Söderqvist, October 23, 1991.

From the very beginning Jerne seems to have suspected a specific antibody, probably for kinetical reasons. Already in April he told Stent that the tryptophane-requiring phage turned into non-tryptophane-requiring ones after "contact with antiphage."[114] Although careful not to confirm this assumption formally in the Göttingen talk in June, he nevertheless used the same notation ("A") for the factor leading to the formation of P-stars and for anti-T4 serum molecules in the reactivation experiments. There is one immediate argument against the assumption that the "A"-factor was an antibody, however. In standard serological and immunological parlance, the term "antibody" denoted a subclass of gamma globulins that form upon the introduction of antigens and have the ability to attach to the antigens and, usually, inactivate them. The factor responsible for P-star formation attached to the antigen, but was not 'against' it; on the contrary, it enhanced the functioning of the antigen – indeed, a rather unusual kind of "anti"body.

Jerne had no use for the metaphysical notion of being 'against' the antigen, however. He took it for granted that the only property that antibodies had in common was their capacity of attaching to antigens. So, it became imperative to prove the specific attachment of the serum factor to the antigen. He recalls that "I made *very sure* that the P* inducing property of these early sera was the property of an anti-T4 antibody."[115] At the end of June 1954, two weeks after his return from Göttingen, he immunized a new horse with a single intravenous injection of 10^{13} T4 phages, and he then took daily blood samples to demonstrate the corresponding increase of the P-star-forming factor in very early serum (days 1 through 8). The result was stunning: P-star formation increased rapidly during the first week of immunization. Jerne felt convinced that the P-star-forming serum factor was a specific antibody, "because they appear in large numbers in serum only after specific immunization of the animal with T4 phage," he wrote in the paper on the P-star phenomenon published a year later.[116] In retrospect, he emphasizes this finding as a "most important point" – the type A antibodies "multiplied a thousandfold . . . immediately upon immunization. They were *not* the ordinary well-known T4 *in*activating antibodies!!"[117]

114. Jerne to Günther Stent, April 10, 1954, Stent papers.

115. Jerne to Ed Goldberg and [?] Karam, February 22–23, 1992.

116. Niels K. Jerne, "The Presence in Normal Serum of Specific Antibody against Bacteriophage T4 and Its Increase during the Earliest Stages of Immunization," *J. Immunol.*, *76* (1956), 214.

117. Jerne to Söderqvist, July 8, 1993.

The identification in early serum of a specific antibody that enhanced the action of T4 phage was itself surprising. But even more surprising was the fact that this antibody was present in small amounts even in normal serum from nonimmunized animals. Jerne apparently did not expect to find it in normal serum, for just a few weeks earlier, when writing the manuscript for the Göttingen meeting, he did not mention the possibility. In the mimeographed proceedings of the meeting, probably in response to a question from the audience, he even added a line to stress that normal sera do *not* produce P-stars.[118] Apparently he reconsidered this opinion, however, because before immunizing the new horse he also drew a blood sample from the nonimmunized animal; furthermore, he did not dilute the serum before mixing it with T4 in the plaque assay. In turned out that even the nonimmunized horse "contained the P* inducing antibody . . . this deeply impressed me," Jerne recalls.[119] Lark vividly remembers the event:

> Well, anyway, he found the antibody went stronger, it was terribly weak, but the most surprising thing was that there was absolutely specific antibody activity in the normal serum.
>
> [Ths: And you were there when he found out?]
>
> Yeah, and he talked about it a bit, I mean he didn't rush, I mean it was typical of Taj that he would be amused by something like that. He would say, of course, "we have to find a way to prove that it is not some kind of artifact," but he was just amused. . . .
>
> [Ths: Did he state it the way you do now?]
>
> No, he said: "it's got activity," and he disappears, and two or three days later working with Perla Avegno he says: "it looks like the activity is specific."[120]

118. Phage Information Service no. 7 (above, n. 109). "This statement, though a mistake, followed because I had experimented only with serum, diluted 1 to 100," says Jerne today (Jerne to Söderqvist, October 23, 1991).

119. Jerne to Ed Goldberg and [?] Karam, February 22–23, 1992.

120. Interview with Gordon Lark, September 17, 1989. "Taj" was Jerne's nickname during the Copenhagen years.

II. NATURAL ANTIBODIES AND THE DARWINIAN CONTEXT

The Crucial Role of the Notion of Natural Antibodies, June–August 1954

"It looks like the activity is specific," was Jerne's remark on his last experimental finding before the generation of the selection theory. Only a week or so after the demonstration of specific P-star-forming antibody activity in normal serum, he made the famous walk over Knippelsbridge. The first preserved draft of the theory is dated August 9, 1954.[121] It is headed "Very Important" (Danish: "Meget Vigtig") and begins:

> *Theory of antibody formation*: Globulin molecules exist in normal serum in a variety of configurations of the aminoacid chain. One or several of these configurations fit, by chance, a given antigen. The antigen, therefore, after injection into the organism *selects* such globulin molecules, and transports these molecules to the cell in which these molecules are prepared for multiplication.[122]

In this first draft Jerne stressed the four major components of the theory: all gamma globulins are also antibodies; all antibody specificities exist already in normal serum; there will always exist some specific antibody that will by chance fit to a given antigen; and the only role of the antigen is to select preexisting specific antibodies.

121. In "Ten Years Later" Jerne dated the discovery event to March 1954, but this draft is from August 9 – i.e., about five months later. Is the draft or the autobiographical account (or are both) wrongly dated? Confronting the problem retrospectively, Jerne is now absolutely sure that he was mistaken with respect to March, and that the selection theory came upon him in July or August. There are several good reasons to accept Jerne's revised dating: Jerne admits that he antedated the discovery event in "Ten Years Later" in an attempt to rule out any possible suspicion that he might have been inspired by Delbrück or others at Caltech, and thereby to establish the fact that he was the sole originator of the theory; and further, all archival sources speak in favor of July or August 1954. For further details, see Thomas Söderqvist, "Biographical Experiments: Using the Contradiction between Autobiographical Stories and the Archival Record as a Resource in Biographical Studies," unpublished paper for session on "Biographies, Biologists, and the History of Biology," International Society for the History, Philosophy, and Social Studies of Biology, Brandeis University, Waltham, Mass., July 15–18, 1993.

122. Jerne papers, box 1954.

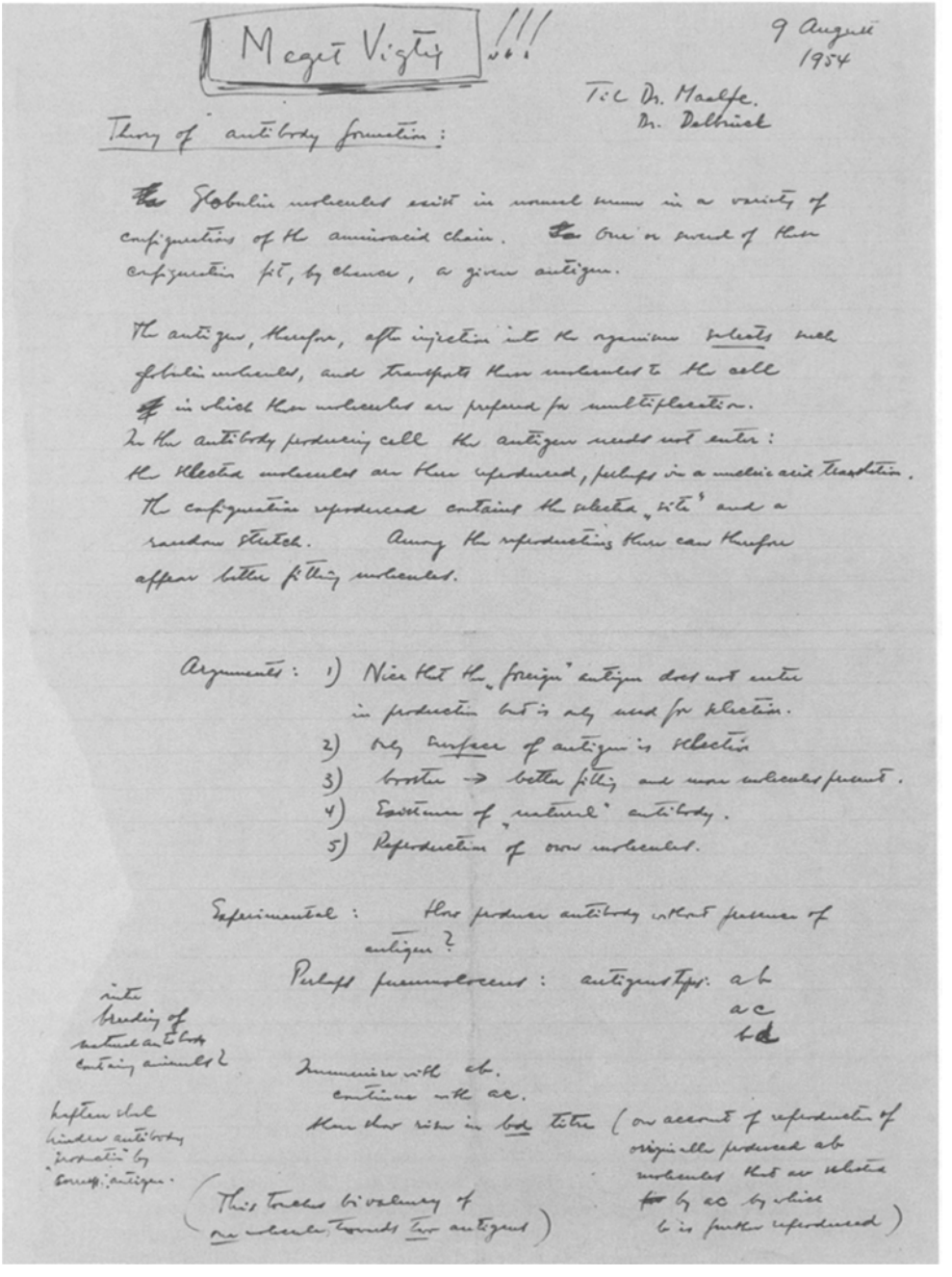

Fig. 1. The first draft of the selection theory of antibody formation, addressed to [Ole] Maaløe and [Max] Delbrück. Jerne often refers to it in conversations as his "last will and testament"; he says that he wrote it right before going to Caltech in mid-August 1954 and that he deposited it in a drawer in his office at the State Serum Institute in Copenhagen to be opened in case he died before he had a chance to write up the paper (several interviews with Jerne, 1987–1991).

Jerne apparently did not say anything about the new theory to Maaløe and Lark before leaving Copenhagen in late August 1954. He planned to talk it over with Delbrück on their trip across the Atlantic, but probably never got the opportunity.[123] Neither Maaløe nor Lark drew any conclusions from the finding of antibody activity in normal serum. They were not immunological novices – Lark had trained with Pappenheimer in New York, and Maaløe had a research background in serology – but neither of them thought in terms of natural selection: "And none of us, even with that fact [the existence of specific antibodies in normal serum], recognized the fact [the selection theory], I can't remember Maaløe, I can't remember myself really understanding the significance of that in any way," Lark recalls.[124] So, why was Jerne "the onlie begetter" of the selection theory?

His former avidity research was evidently of great importance. Although Jerne sometimes downplays the role of the avidity phenomenon in the origin of the selection theory of antibody formation, it nevertheless occupied a central position in his awareness during the first ten years of his scientific career. The avidity work gave him the experimental tool that enabled him to find a specific antibody in normal serum. Yet the problem of avidity increase during immunization was still a mystery. Why did the antibodies become more "avid" after the second shot? Why did "late" sera neutralize the antitoxin better than "early" sera? The change in avidity during immunization was an anomaly to the template theories, and it continued to provide an enigma to be explained – we can see it as an explanandum event in constant search of an explanans. The selection theory immediately explained the phenomenon of avidity increase and removed its anomalous character.[125] In the first written sketch of the theory, Jerne refers to "better fitting" as one of the major arguments for the theory, and he was seemingly impressed by the power of the selection theory to explain the increase in avidity during immunization.

123. "Unfortunately," he writes, "the atmosphere did not seem to permit rather far-fetched theories of antibody formation to get more than scant attention" (Jerne, "Ten Years Later" [above, n. 12], pp. 304–305.

124. Interview with Gordon Lark, September 17, 1989.

125. In primary stimulus the antigen (e.g., a bacterium) finds only a few natural antibodies, showing various degrees of affinity to the antigenic structures. During the later stimulus, when the selected molecules have been replicated in larger numbers, "the antigen will find a large concentration of globulin molecules fitting all its surface patterns and will preferentially carry those which show the highest combining capacity to the globulin-reproducing cells" (Jerne, "Natural-Selection Theory" [above, n. 9], p. 850).

Neither the avidity phenomenon nor the observation of an increase in avidity during the course of immunization, by themselves, however, impelled Jerne to formulate the selection theory; although these phenomena provided the explanandum events, they did not contribute positively to the formulation of the explanans. In retrospect, Jerne maintains that the "avidity observations" strengthened his "faith in the truth of antibody selection."[126] His assertion echoes similar testimonies, for example by Stent, who says that "the thing that impressed me immediately was the avidity story . . . that the avidity increases. Nobody could explain that thing. And that, to me, was an obvious proof that there was an evolutionary phenomenon . . . first of all you find spontaneously things that fit very poorly, you give the antigen and then, not only does the titre go up, but the quality. And this could not be explained by the Pauling type of theory."[127] It is likely, therefore, that the explanatory power of the selection theory reinforced Jerne's belief in it during the gestation period. Using Kenneth F. Schaffner's distinction between a "logic of preliminary evaluation" and a "logic of generation,"[128] we may say that the avidity experiments functioned as an element in the "logic of preliminary evaluation" of the theory, but they hardly played any significant role in its "logic of generation."

The last experimental event that preceded the formulation of the selection theory was the finding of antibody activity in normal serum: "These observations . . . led to speculation about the mechanisms of antibody formation," Jerne wrote a year later.[129] The observation has usually been interpreted as being identical with the finding of a natural antibody. For example, it has been maintained that the finding of a natural antibody was "the major empirical finding impelling Jerne to his theory."[130] But the existence of a natural antibody was not an empirical finding: the experiments in late June and early July 1954 did not demonstrate the existence of a natural antibody, only antibody activity in normal serum. The existence of a natural antibody was rather an *interpretation* of the empirical finding of antibody activity in normal serum.

126. Jerne, "Ten years Later" (above, n. 12), p. 302.
127. Interview with Günther Stent, November 1, 1988.
128. Schaffner, "Discovery" and *Discovery* (both above, n. 36).
129. Semiannual report to the Polio Foundation, 1955, Jerne papers, box 1955.
130. Schaffner, "Discovery" (above, n. 36), p. 196. This statement has been repeated by, among others, Peter Keating and Abdelkérim Ousman, "The Problem of Natural Antibodies, 1894–1905," *J. Hist. Biol.*, *24* (1991), 245.

Therefore, it is probably no coincidence that Jerne carefully titled his paper on the P-star formation "The Presence in Normal Serum of Specific Antibody . . ." and not "The Presence of a Natural Antibody. . . ."[131] As he himself realized, there were in fact two possible interpretations of the experimental demonstration of the P-star-forming antibody in normal serum: the antibody activity could be explained by assuming "either that they were spontaneously produced by the animal, or that practically all normal animals have been exposed to and have responded to T4 antigen."[132] Jerne chose the first alternative. One could not disprove the possibility that the animals had been exposed to T4, he wrote, "but the present author prefers the hypothesis of spontaneous production, i.e., that normal sera contain among their γ globulin molecules a fraction of less than one to one million that happens spontaneously to have a specific configuration of the A type."[133]

There was one substantial argument against the natural antibody interpretation: as Jerne wrote to Maaløe shortly after his arrival at Caltech, "unfortunately, one can of course always argue that the horse has met T4 earlier on its way in life."[134] This was in the days before the widespread use of germ-free animal quarters, and, as Jerne points out in a later interview, "[t]hey said that the animal has probably been exposed to that antigen anyway, without our knowing it."[135] Finally, except for vague hints and an occasional mention in the correspondence, there are no notes on natural antibodies among Jerne's papers, and no experiments recorded in the laboratory protocols. He had not been confronted with the enigma of natural antibodies in his daily research practice, as he had been with the avidity phenomenon. Yet he chose to interpret the finding of antibody activity in normal serum as the presence of a natural antibody, and he did not give any further arguments in the P-star paper for this option other than that – he "preferred" it.[136]

131. Jerne, "Presence in Normal Serum" (above, n. 116), p. 215.

132. Ibid.

133. Ibid.

134. "[M]an kan jo altid indvende at Hesten tidligere paa sin vej har mødt T4, desværre" (Jerne to Ole Maaløe, October 16, 1954).

135. "De sagde dyret har nok alligevel været udsat for det antigen, bare uden at vi ved det" (interview with Jerne, April 27, 1987).

136. In the *PNAS* paper, however, Jerne argued (with reference to W. W. C. Topley, *An Outline of Immunology* [London, 1935]) that since normal serum contains so many different antibodies against a variety of bacteria, it is difficult to imagine that they are all the result of infection, particularly since these bacteria did not occur in the animal's natural environment. He also cited the conclusion from experimental evidence of R. Doerr (*Antikörper*, vol. IV of *Die Immunitätsforschung: Ergebnisse und Probleme in Einzeldarstellungen*, ed. R. Doerr

The finding of a P-star-forming antibody in normal serum and the subsequent interpretation of this finding as a natural antibody can hardly constitute the "foundation" for a logic of generation of the selection theory, as Keating and Ousman have suggested.[137] The finding of the P-star-forming antibody was unexpected, but not enough to "impel" Jerne to the theory; hundreds of serologists had observed antibodies in natural serum before him, but nobody had taken the step of "preferring" the natural antibody interpretation without any further argument. Why did Jerne "prefer" to interpret the P-star-forming antibody activity as the existence of a natural antibody? Obviously, this is the endpoint in the textual and logical reconstruction story. To go beyond this point, we must have recourse to other explanatory resources. In the following paragraphs I will try to reconstruct some of the cultural and intellectual contexts that Jerne encountered in his readings and interaction with other people, which may bring us further toward and understanding of his "preference."

The Context of Theoretical Tradition: Jerne's Relation to the Instruction Theories of Antibody Formation

Theoretical traditions, paradigms, schools of thought, and so on constitute a most important intellectual context for the generation of new theories. They are there for imagination to feed upon, or as objects for critique and dismissal. Although Jerne, like everyone else in the world of serology and immunology at the time, was well aware of the standard textbook accounts of Ehrlich's side-chain theory and the template theories, theories of antibody formation seem to have played a rather small role in his avidity work in the 1940s and early 1950s. He did not undertake his experiments on the kinetics of the phage-antiphage reaction to prove or test the one or the other theory. He seems, rather, to have been driven first by a wish to demonstrate the validity of a physical-chemical approach to the avidity phenomenon, and later, when he applied bacteriophage to serology, by a wish to show that the

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[Vienna: Springer-Verlag, 1949]): "We must accept that it has been definitely demonstrated that natural antibodies can develop without an antigenic stimulus, and that this spontaneous formation is by far the most frequent origin of natural antibodies" (Jerne, "Natural-Selection Theory" [above, n. 9], p. 852).

137. Keating and Ousman claim that "natural antibodies have played a central role in the development of immunology as a discipline insofar as their presence has been considered both an anomaly for 'instructive' theories of antibody formation, and a *foundation* of 'selective' theories" ("Problem" [above, n. 130], p. 245; my emphasis).

molecular biologists were wrong in their belief in the irreversibility of the phage-antiphage reaction. The problem of antibody formation does not seem to have been continuously on his mind, as was the avidity problem; in fact, the archive contains almost no notes about antibody formation before the "Very Important" draft in August 1954.

This does not imply that Jerne was indifferent to theoretical issues in general, or to theories of antibody formation in particular. On the contrary, he took an early stand against template theories. The former head of the Department of Standardization, Johannes Ipsen, recalls that Jerne read Pauling's seminal 1940 paper during the war.[138] Hans Noll, who wrote his dissertation in the department, says that he saw Pauling's paper on Jerne's desk in the fall of 1949, and that Jerne discussed the theory with Maaløe: "what I remember distinctly," says Noll, "is that he [Jerne] was questioning this [theory] . . . I have a distinct recollection that he disagreed."[139] Jerne himself recalls that he thought from the very beginning that Pauling's theory was "ridiculous,"[140] and that template theories were "extremely distasteful" to him.[141] So, even if he did not have any alternative in mind, the template theories nevertheless formed a central part of his intellectual heritage as an object of critique.

One plausible reason why Jerne "preferred" the natural antibody interpretation is that it would provide a blow against Pauling's theory. Natural antibodies were well known: they had been postulated theoretically by Ehrlich, in the form of preformed-side-chains, and they had been a well-established phenomenon in the serological literature for decades. With the decline of Ehrlich's theory in the 1920s, natural antibodies had been widely "dismissed as theoretical impossibilities,"[142] since antibodies were thought to be formed de novo on the arrival of the antigen. For a couple of decades the specificity of these natural antibodies "was questioned, their provenance mysterious, and their very existence neglected in the main by the proponents of instruction theories of antibody formation."[143] By the 1940s and early 1950s, natural antibodies were firmly relegated to the footnotes of the serological and immuno-

138. Pauling, "Theory" (above, n. 5); interview with Johannes Ipsen, March 17, 1987).

139. Interview with Hans Noll, September 12, 1989.

140. "Jeg syntes de var latterlige lige fra starten" (interview with Jerne, May 5, 1987).

141. Jerne to Kenneth F. Schaffner, March 28, 1978.

142. Keating and Ousman, "Problem" (above, n. 130), p. 245.

143. Silverstein, *History* (above, n. 1), p. 116.

logical literature. This is probably the reason why the faculty opponent reacted so strongly against Jerne's flirtation with the idea of preformed antibodies in his dissertation (see above, Section I).

Jerne was, of course, well aware of this enigmatic phenomenon. For example, he recalls that "the serological diagnosticians told me that they 'started' with serum-dilutions 1:10. 'If we start with undiluted serum we get too many false-positives'!"[144] I have already mentioned his reference, in the dissertation in 1951, to Holt's suggestion that normal serum might contain preformed antibodies. Moreover, he recalls "[a] book called 'Natural Antibodies' by R. Doerr, then professor in Basel, [who] discussed these questions, about 1948," implying that this book made an impression on him at the time.[145] But to read about natural antibodies in the literature was one thing; to see them in the test tube in one's own laboratory was another matter. Given his negative view of the template theories and the surprising finding of a specific antibody in normal serum, it is reasonable to assume that the natural antibody interpretation seemed to Jerne the only logical one. It is probably no coincidence that the first archival evidence of his interest in theories of antibody formation dates from the same time period. On July 1, 1954, right after he started immunizing the new horse, he wrote to Stent about the latest P-star experiments and concluded: "only if some of this could lead to an attack on antibody production there would be something of . . . central importance."[146]

Another reason why Jerne found the template theories "ridiculous" was the assumption, first made by Landsteiner, that the number of antigens is infinite. Landsteiner had demonstrated that an organism can produce antibodies against any possible antigen, and had used this as an argument against Ehrlich's theory: a rather limited number of different preformed side-chain specificities could not, he said, take care of an "infinite" number of antigens.[147] Jerne did not like the infinity assumption. "Having studied some thermodynamics (in Leiden)," he says, "I became irritated at [Landsteiner's] conclusion that the potential to produce antibodies is 'infinite,' which had led to the template theories."[148] The number of antigens is not infinite, it is just a large number: "Even if (what I think very unlikely) as many haptenic groups of different speci-

144. Jerne to Pauline Hogeweg and Rob de Boer, March 29, 1989.
145. Ibid. Jerne refers to Doerr, *Antikörper* (above, n. 136).
146. Jerne to Günther Stent, July 1, 1954, Stent papers.
147. Landsteiner, *Spezifizität* (above, n. 3).
148. Jerne to Pauline Hogeweg and Rob de Boer, March 29, 1989.

ficity could be synthesized as there are names in the New York telephone directory," he later wrote to Haurowitz, "this would amount to only about one million, whereas the number of globulin molecules in the blood of a rabbit is more than a million times a million times a million."[149] Furthermore, since the antibody does not have to fit exactly to the antigen, a finite number of antibody specificities, say one million, would be enough to take care of all possible antigens. Jerne ventures to say that his dislike of this infinity argument was in fact one of the major sources of inspiration for the Knippelsbridge event:

> I had been pondering a long time whether it would be possible to find a flaw in the argument behind the instruction theories. And one evening, when I walked home from the Serum Institute to Amaliegade, I think it was on Knippelsbridge, it suddenly struck me that the fundamental flaw was the word 'infinite.' And as an old mathematician I thought it was irritating to use the word 'infinite.' Nothing is infinite.[150]

Hence, thinking in terms of finiteness is not only a persistent trait of the theory, but also a significant part of the biographical understanding of the origin of the selection theory. Jerne is "le chevalier du fini," as Anne Marie Moulin calls him in *Le dernier langage de la médicine.*[151]

A Revival of Ehrlich?

Thus, Pauling's template theory was mainly a negative theoretical context for the generation of the selection theory: it provided a "distasteful" theoretical adversary, but it did not in itself provide

149. Jerne to Felix Haurowitz, March 28, 1956.

150. "Jeg havde i længere tid grublet om ikke det ville være muligt at finde en tankefejl i den argumentation, der ligger til grund for instruktionsteorierne, Og en aften jeg spadserede hjem fra Seruminstituttet til Amaliegade, jeg tror det var på Knippelsbro, slog det pludseligt ned i mig at den grundlæggende fejl i argumentationen må være ordet uendelig, det er uendeligt mange antistoffer. Og som gammel matematiker syntes jeg allerede at det var irriterende at man ville bruge ordet uendelig. Intet er uendeligt" (interview with Jerne by Jørgen Rygaard, Danish Radio, 1971, transcribed by Lotte Juul Nielsen).

151. In her unpublished dissertation at the University of Lyon, Moulin called Jerne "le chevalier du infini" – that is, the opposite of finite. As faculty opponent, Jerne strongly objected to this characterization (Jerne papers, box 1988). In the book version of the dissertation, Moulin revised her label of Jerne and now calls him "le chevalier du fini" (Moulin, *Dernier langage* [above, n. 35], p. 276).

any positive ideas for imagination to feed on. There existed another theoretical tradition that *could* provide a positive impetus, however: Ehrlich's side-chain theory. Although long-since dismissed, it belonged to the basic curriculum of all serologists and immunologists at the time and provided potentially better food for theory generation. Was Jerne just reviving the tradition of preformation? Several immunologists thought that he had "resurrected the selective principle [of Ehrlich],"[152] and that the selection theory was "basically similar" to the side-chain theory.[153]

In his survey of the history of immunology, Arthur Silverstein concludes that "Jerne revived the old Ehrlich concept," and finds it "curious" that Jerne did not refer to Ehrlich in the *PNAS* paper.[154] Haurowitz, one of the original proponents of template theories, was of the opinion that Jerne had taken over Ehrlich's "Anschauung über präformierte Rezeptoren in einer neuen Form,"[155] and he even confronted Jerne personally a few months after the publication accusing him of repressing the reference to Ehrlich. Later he wrote:

> Als er [i.e., Jerne] seine Theorie der Antikörperbildung veröffentlichte, fiel mir auf, daß er mit keinem Wort Ehrlich erwähnte trotzdem sich seine Theorie von jener Ehrlich's nur ganz unwesentlich unterschied. Er nahm Gegenwart der "Rezeptoren" in der Zirkulation an, während Ehrlich sie als zellgebunden annahm. Ich fühlte ein Unrecht gegen Ehrlich und schrieb daher an Jerne, den ich persönlich nicht kenne.[156]

Jerne answered politely, saying he was "sorry now that I did not mention Paul Ehrlich in my paper," but he did not think the two theories were particularly similar, "and as my manuscript . . . had to be short I could not include a historic account of antibody formation theories"; it was true that Ehrlich had assumed preformed antibodies, "[b]ut is this a sufficient reason to call his theory 'very similar' to mine?" Jerne asked.[157] It made sense to differentiate between selection theories and instruction theories, but theories

152. G. J. V. Nossal, "Genetic Control of Lymphopoiesis, Plasma Cell Formation, and Antibody Production," *Internat. Rev. Exp. Pathol., 1* (1962), 51.

153. Talmage, "Allergy and Immunology" (above, n. 18).

154. Silverstein, *History* (above, n. 1), p. 77.

155. Haurowitz, "Biosynthese" (above, n. 11), p. 62.

156. Quoted in letter from Richard Prigge to Jerne, October 5, 1960.

157. Jerne to Felix Haurowitz, March 28, 1956. The length of the manuscript was restricted by the editorial rules of the *PNAS*.

within each of these groups were not necessary similar: "Diese Idee der *spontanen* ('random') Vorbildung der Antikörper, und denn selektiven *Reproduktion*, schien mir damals ganz von Ehrlich's Theorie abweichend," Jerne wrote a few years later.[158] He did not assume, as Ehrlich did, that antibodies have other functions, such as nutrient uptake, and he believed that the difference between selection of circulating antibodies and selection of cell receptors was considerable: "I did not place receptors (Burnet did this) on cells, which was the crux of Ehrlich's side-chain concept," he says.[159] To refer to Ehrlich would have been as if Einstein had felt obliged to refer to Newton, he thought, as if "die EINSTEIN'sche Theorie, die zweifellos eine Fortbildung der NEWTON'schen Theorie ist, nur dann hätte herausgebracht werden dürfen, wenn der aller Welt bekannte Name von NEWTON an den Anfang der ersten Publikation gesetzt worden wäre."[160]

But even though Jerne did not think that his theory was particularly similar to that of Ehrlich, he may nevertheless have been inspired by Ehrlich's notions of preformation and the passive role of the antigen. In fact, during his stay at Caltech in 1954–1955 he made a couple of notes on Ehrlich's side-chain theory with special reference to the function of the antigen. "The most radical view" of all theories of antibody formation with respect to the role of the antigen, he wrote,

> is the original Ehrlich side-chain theory which assumed that antibodies of all kinds were already present on the cells. . . . though since long regarded as obsolete, this theory has the advantage of radically dismissing any indirect inducing action of the antigen. . . . This theory [i.e., the selection theory] is remarkable because it does not entertain the later notion of the active role of the antigen . . . its basic idea seems less prejudiced than its modern successors.[161]

158. Jerne to Richard Prigge, undated (between October 5 and December 1960).

159. Jerne to Arthur Silverstein, June 8, 1985. Today Jerne adds: "Ehrlich and his contemporaries (Zeitgeist) *could not* imagine that the body would produce *proteins that were useless*, produced 'at random.' Therefore Ehrlich had to give the Seitenketten an important function, namely to give cells their nutrient molecules" (Jerne to Söderqvist, July 8, 1993).

160. Quoted in Richard Prigge to Jerne, December 1, 1960.

161. Undated note (Jerne papers, box 1954–1955). The notes were evidently written during his stay at Caltech because they are written on American-size stationery, which he had never used before.

So, evidently, when writing his manuscript Jerne was well aware of the similarity between his and Ehrlich's theory with respect to the role of the antigen. To Haurowitz he explained, however, that he "did not consciously derive" the selection idea from Ehrlich,[162] and thirty years later when again asked about the connection, he did not remember his Caltech notes on Ehrlich: "Let me first give you the simple and true answer: it did not even occur to me! In retrospect, you may find this hard to believe. In 1956, I went to WHO, Geneva, and it was only a year or so later that some one pointed out to me (perhaps it was Talmage) that my theory was similar to that of Ehrlich."[163] Hence, it is reasonable to ask, as Silverstein does, why Jerne did not mention Ehrlich in the published paper.

Jerne's Caltech notes on Ehrlich were written two months (at the earliest) after the discovery event, so we cannot conclude that Ehrlich's theory played any significant role in the chain of thoughts leading to the Knippelsbridge event earlier that summer. There are no other indications in favor of Jerne's having been inspired by Ehrlich's side-chain theory, so the claim that he "revived the old Ehrlich concept" cannot be substantiated. As Frederic L. Holmes strongly recommends, "the historian should not discount the testimony of his or her subject without compelling reason."[164] Thus, Jerne's Caltech notes on Ehrlich are best interpreted as an element in the preliminary evaluation of the theory and as yet another reinforcement of his long-term fascination with the notion of preformation. From the point of view of the logic of generation of the selection theory, the Ehrlich tradition seems to have been rather unimportant, particularly in comparison with other intellectual traditions – for example, the Darwinian idea of natural selection.

The Local Darwinist Context: The Biometricians and the Phage Group

The selection theory of antibody formation contains a significant random element, particularly when compared to the preceding template theories, which were strictly deterministic: "Among the population of circulating globulin molecules," Jerne wrote in the *PNAS* paper, "there will *spontaneously* be a fraction possessing

162. Jerne to Felix Haurowitz, March 28, 1956.

163. Jerne to Arthur Silverstein, June 8, 1985.

164. Frederic L. Holmes. *Hans Krebs, vol. II, Architect of Intermediary Metabolism, 1933–1937* (New York: Oxford University Press, 1993), p. 429.

affinity toward any antigen. . . . The introduction of an antigen . . . leads to the selective attachment to the antigen surface of those globulin molecules which *happen* to have a complementary configuration."[165] He did not stress the notion of randomness and the role of probabilistic thinking in the origin of the theory in "Ten Years Later," but in later statements he has put more emphasis on these aspects: "the most important [aspect of the theory] is not selection, but randomness," and "the basic idea [of the theory] is chance," he says in recent interviews.[166] He even elevates chance and randomness to the distinctively innovative trait of the theory: "I think that I was the first to point out the importance of a *random* element . . . [which] now seems to me the most important departure from earlier paradigms."[167]

Jerne's positive evaluation of the role of randomness also points to an important social context for the selection theory: his scientific training. One of his first tasks after being employed at the Serum Institute in 1943 was to test whether the data from biological assays of toxins and antitoxic sera were normally distributed, and he demonstrated his talents by inventing a new graphical method for evaluating the normal distribution.[168] Ipsen remembers this work as "a party game more than a really serious work,"[169] but subjectively it seems to have had a decisive effect on Jerne's future scientific development. In fact, he refers to this experience as his essential departure into science, maintaining that "[it] was the first time I realized that I was smarter then he [i.e., Ipsen] and it made me somewhat Watsonistic."[170] After having spent most of the autumn of 1943 reading books on the subject – particularly R. A. Fisher's *Statistical Methods for Research Workers*, which he referred to as "a 'Bible' in this field,"[171] – he attended Georg Rasch's statistical lectures at the university. In the following years, Jerne received a thorough training in statistics. His research work, both the routine standardization work and his dissertation work on avidity, became increasingly statistically oriented, and he spent

165. Jerne, "Natural-Selection Theory" (above, n. 9), p. 849 (my emphasis).

166. "[D]et væsentligste ikke selektion, men randomness"; "grundidéen i den er tilfældigheden" (interviews with Jerne, April 23, 1987, and December 8, 1986).

167. Jerne to Debra Jan Bibel, October 8, 1986.

168. Johannes Ipsen and Niels K. Jerne, "Graphical Evalution of the Distribution of Small Experimental Series," *Acta Pathol., 21* (1944), 343–361.

169. "[E]n selskabsleg, mere end egentlig et alvorligt arbejde" (interview with Johannes Ipsen, March 17, 1988).

170. "Det var første gang at det gik op for mig at jeg var klogere end ham [i.e., Ipsen], og det gjorde mig sådan lidt 'Watsonistisk' " (interview with Jerne, May 5, 1987); the expression "Watsonistic" refers, of course, to James D. Watson.

171. Jerne to Tjek Jerne, July 12, 1943.

much time conversing with Rasch and another statistician, Michael Weis Bentzon of the Institute's Department of Statistics. In the late 1940s he coauthored a paper on statistical problems in biological assays,[172] and he began to identify himself professionally as a biostatistician to the extent that he was elected to the Council of the Biometric Society in 1951. In the early 1950s he also took initiatives to establish a Scandinavian-Dutch regional branch of the society and to found a biometrical discussion club in Copenhagen.[173]

So, Jerne's later contention – that he came to immunology at the age of forty "steeped in fantasies about randomness and diversity"[174] – is well substantiated. His long-established biometrical experience and his habit of thinking in terms of hazard and chance can be seen as diffuse cognitive resources that could be mobilized at any moment, and that therefore played a significant role in the formulation of the selection theory. He could also have added "number fantasies," for there is a strong number element in the selection theory: "a million structurally different antibody-combining sites would suffice to explain serological specificity; if all 10^{17} gamma-globulin molecules per ml of blood are antibodies, they must include a vast number of different combining sites, because otherwise normal serum would show a high titer against all usual antigens."[175] In later autobiographical fragments, Jerne in fact even ventures to say that reasoning in terms of numbers was the specific factor that led him to the natural antibody ideas and to the multiplicity of specificities.[176] Number games and combinatorics have been persistent themes in many of his later works, and prime numbers have been his favorite pastime for decades.

The selective mechanism is the central and most radical element of the new theory, and the notion that impressed most of his contemporaries. The avidity phenomenon had "Darwinian overtones," as Jerne writes in "Ten Years Later."[177] One of the reasons why

172. Niels K. Jerne and E. C. Wood, "The Validity and Meaning of the Results of Biological Assays," *Biometrics*, *5* (1949), 273–299.

173. Jerne papers, box 1951 and box 1952.

174. Undated note, probably 1985, Jerne papers, box 1985.

175. Jerne, "Ten Years Later" (above, n. 12), p. 301.

176. Jerne papers, box 1985.

177. Jerne, "Ten Years Later" (above, n. 12), p. 303. Today, Jerne claims that he was the first to use Darwinian ideas to explain physiological and biochemical phenomena: "Darwinian 'selection of the fittest' had hitherto been applied only with regard to the diversity of plant and animal speciees. I think I was the first to propose that the Darwinian selection principle was also possible and indeed applied, within the diversity of cells within a single polycellular organism, i.e. 'physiologically' " (Jerne to Söderqvist, July 8, 1993).

Burnet – who remained a spare-time naturalist and a devoted evolutionist throughout his life[178] – responded so favorably to Jerne's *PNAS* paper was presumably the Darwinian thrust of the theory, which stood in sharp contrast to the Lamarckist overtones of the template theories. Does this suggest that Jerne's preference for interpreting the occurrence of antibodies in normal serum as natural antibodies, and his subsequent discovery of the selection theory, could be understood against the background of the Darwinian idea of natural selection?

Jerne himself does not consider the Darwinian context to be of much interest for an understanding of the origin of the theory: "Of course I thought of Darwin, I called it natural selection theory," he says, adding that "everybody was aware of Darwin, so it is not a clue."[179] If, by "everybody," Jerne means the scientific zeitgeist of the time, he is probably right that Darwinism is not a clue; although a knowledge of Darwin and natural selection was a part of general education, the renaissance of Darwinian thinking in terms of the neo-Darwinian synthesis was not yet generally accepted beyond a small group of geneticists and evolutionary biologists.[180]

But if by "everybody" is meant the scientists whom Jerne respected most at the time, Darwinism nevertheless becomes a clue to the origin of the selection theory. R. A. Fisher, one of the originators of the neo-Darwinian synthesis who promoted the revival of the concept of natural selection, was, as already mentioned, one of Jerne's most important significant others. Jerne was well acquainted with Fisher's work and met him in 1949 at the Second International Biometric Conference. Jerne had studied Fisher's statistical works intensely in the mid-1940s and was therefore most probably also well acquainted with *The Genetical Theory of Natural Selection*.[181] Fisher's book was explicitly written from the standpoint of a physicist; since Jerne was trained in physics and had approached the avidity problem with the attitude of a physical chemist, it is reasonable to assume that he was positively inclined toward its treatment of natural selection, especially as Fisher's emphasis on the "remarkable resemblances" of the fundamental theorem of natural selection to the second law of thermodynamics was very much in line with Jerne's way of thinking about sero-

178. Christopher Sexton, *The Seeds of Time: The Life of Sir Macfarlane Burnet* (Oxford: Oxford University Press, 1991).

179. Interview with Jerne, April 23, 1987.

180. See V. B. Smocovitis, "Unifying Biology: The Evolutionary Synthesis and Evolutionary Biology," *J. Hist. Biol.*, *25* (1992), 1–65.

181. R. A. Fisher, *The Genetical Theory of Natural Selection* (Oxford, 1930).

logical phenomena in terms of physical chemistry. In addition, the fact that Jerne explicitly, both in the *PNAS* paper and in the early drafts of the theory, used population dynamics concepts – "globulin population," "population pressure," and others – supports the impression that he was speaking the same language as those who were working on natural selection and population dynamics.[182]

Among the scientists with a Darwinist bent in Jerne's immediate social circle were also Delbrück and other members of the phage group. Several of early molecular biologists were among the active promoters of a selectionist view in biology.[183] Delbrück had shown an active interest in Fisher's theory of natural selection: he had given lectures on *The Genetical Theory of Natural Selection*, and he had even tried to establish research cooperation between German physicists and biologists on the basis of Fisher's ideas before emigrating to the United States in the late 1930s.[184] With the famous fluctuation experiment of Salvador E. Luria and Delbrück, molecular biology appeared, finally, "to be cleansed of the last traces of Lamarckian thought."[185] Jerne and Maaløe frequently discussed this work, and in December 1948 Jerne corresponded with Luria about a couple of statistical problems;[186] he was therefore well acquainted with the fluctuation experiment already in the late 1940s. Today it "occurs" to him that

> the Delbrück-Luria fluctuation test which had so deeply impressed me prior to 1950, probably prepared my mind for the selection theory of antibody formation. The fluctuation test showed that penicillin does not teach bacteria to become penicillin resistant. In a deep sense of analogy, there is a similarity

182. In a letter to Maaløe, Jerne wrote: "The details can be anyway – the main point in my idea is that the function of the antigen is to exert a population pressure on the distribution of a heterogeneous globulin population" ("Detaljerne kan være hvordan somhelst – hovedsagen i min ide er at antigenets funktion er at udøve et populationstryk paa distributionen af en heterogen globulinpopulation. Tages antigenet bort gennem lang tid glider populationen tilbage"; Jerne to Maaløe, October 16, 1954).

183. See Evelyn Fox Keller, "Between Language and Science: The Question of Directed Mutation in Molecular Genetics," *Perspect. Biol. Med.*, *35* (1992), 292–306.

184. Ernst Peter Fischer and Carol Lipson, *Thinking about Science: Max Delbrück and the Origins of Molecular Biology* (New York: Norton, 1988).

185. Keller, "Between Language and Science" (above, n. 183), p. 293; S. E. Luria and M. Delbrück, "Mutations of Bacteria from Virus Sensitivity to Virus Resistance," *Genetics*, *28* (1943), 491–511.

186. Jerne to Luria, December 7, 1948; Luria to Jerne, December 21, 1948.

> to the assumption that antigen does not instruct or teach [the] cell to make specific antibodies but that these antibodies are already present before the antigen arrives.[187]

There is even some circumstantial evidence to support the suggestion that Jerne had particular reason to pay attention to the Darwinian idea of natural selection in the spring and summer of 1954 – namely, after the arrival of the March issue of the journal *Biometrics*. He had earlier contributed to the journal and still subscribed to it, and he may have read this issue with particular interest since Fisher was involved in a debate about different transformation methods for the analysis of variance, a topic that concerned some of the standardization problems that Jerne had been working on earlier.[188] The footnotes of Fisher's paper gave references to earlier papers in *Biometrics* dealing with natural selection (otherwise a rare subject in the journal's pages),[189] and it is tempting to believe that the paper and the subject were brought up during Delbrück's visit, either in Copenhagen in late March 1954, or in Göttingen a few months later.

The evidence for a local convergence of selectionist ideas in Copenhagen in the spring and early summer of 1954 is only circumstantial. But – give the fact that Fisher and Delbrück were two of Jerne's intellectual heroes as well as ardent selectionists, given that Delbrück and Jerne had a common interest in Fisher's ideas, and given the high probability that Jerne read the *Biometrics* issue and may have discussed it with Delbrück, for example in Göttingen in June – the Darwinian idea of natural selection was most likely actualized in Jerne's mind in the months right before the Knippelsbridge event. This circumstantial evidence, together with Jerne's own account, reinforces the impression that his personal contacts with scientists oriented toward selectionist and Darwinian thinking constitute one of the important contextual elements in a revised narrative of the origin of the selection theory.

CONCLUDING REMARKS

Niels K. Jerne's autobiographical essay on the origin of the selection theory of antibody formation in 1954–1955 has already become one of the classic eureka stories in the history of contemporary

187. Jerne to Söderqvist, January 19, 1991.

188. R. A. Fisher, "The Analysis of Variance with Various Binomial Transformations," *Biometrics*, *10* (1954), 130–139.

189. R. A. Fisher, "Gene Frequencies in a Cline Determined by Selection and Diffusion," *Biometrics*, *6* (1950), 353–361.

life sciences. In the present study, the origin of the selection theory has been reconstructed on the basis of Jerne's private and scientific papers and of interviews with some of the key historical actors. The result is a rather different version of the importance of the different cognitive and contextual elements in the origin narrative.

Whereas Jerne and his later interpreters downplay the importance for the origin of the selection theory of his earlier research on the avidity phenomenon, I conclude that the attempt to understand avidity – a problem that grew out of the classical serological tradition – constituted his long-term research program and the major empirical basis of the selection theory. Everything that Jerne did before the formulation of the theory, he did in terms of understanding avidity. Although the avidity work hardly played any significant role in the logic of generation of the selection theory, it was a key element in the logic of preliminary evaluation. (In contrast, Burnet, in his clonal modification of Jerne's theory, asserted that its great virtue was that it provided an approach to the distinction of "self from not self."[190] Thus, the two major founders of the basic dogma in contemporary immunology evaluated the main virtues of the selectionist revolution in widely different ways.)

In his 1966 essay Jerne also elaborated on the importance of the intellectual impact of the members of the phage group who visited the Danish State Serum Institute in the early 1950s: they provided him with a stimulating intellectual ambience, and they strengthened his self-esteem. Another significant impact of the phage group for the conception of the selection theory was that they delivered a new tool for his research; by implementing a bacteriophage-antiphage plaque assay system as a simple and extremely sensitive method for detecting small amounts of excess antigen, Jerne was able to demonstrate the reversibility of the antigen-antibody reaction, and thus to prepare the ground for the subsequent finding of antibody activity in normal serum.[191]

It has earlier been suggested (e.g., by Schaffner), that the notion of natural antibodies was the major empirical finding that impelled Jerne to his theory.[192] In this paper I have argued that the natural

190. Burnet, "Modification" (above, n. 21).

191. For a discussion of the importance of choosing the right organism for experimental work, see Adele E. Clarke and Joan H. Fujimura, eds., *The Right Tools for the Job: At Work in Twentieth-Century Life Sciences* (Princeton: Princeton University Press, 1992).

192. Schaffner, "Discovery" and *Discovery* (both above, n. 36); Ousman, "Problem" (above, n. 130).

antibody was not an empirical finding per se, but rather an *interpretation* of a real empirical finding – namely, that of antibody activity in normal serum. When Jerne discovered normal serum antibody activity in June 1954, he was confronted with the choice between two rival interpretations: the activity could be the result of earlier exposure to antigens (the obvious interpretation according to instruction theorists), or it could be the result of the spontaneous production of natural antibodies.

Jerne "preferred" the second interpretation. His preference for the natural antibody interpretation, and his subsequent formulation of the selection theory of antibody formation, cannot be accounted for solely by reference to a logical reconstruction of the chain of events. Rather, in order to illuminate why he chose to think in terms of random selection of natural, preformed antibodies, one must also have recourse to the cultural and personal contexts of Jerne's work. In this paper, I have restricted the discussion to the immediate social and intellectual context.

For example, Jerne dismissed the instruction theories partly because he was trained in physical chemistry and was used to operating with large numbers, and therefore did not believe in the idea of an infinite number of antigens. He also had long experience with biometrical research and an interest in number games and combinatorics, and his habit of thinking in terms of chance was a cognitive resource that could be mobilized in the generation of an alternative theory.

The Darwinian context is downplayed by Jerne, but there is ample circumstantial evidence (for example, his close, personal connections with two major exponents of selectionist thinking of the time, R. A. Fisher and Max Delbrück) for the fact that selectionist thinking was part of his local, cultural setting. Hence, the contextual origin of Jerne's natural selection theory parallels that of Burnet's modification of it into the clonal selection theory; another reason why Burnet found Jerne's idea so titillating was that it resonated with his own long-term Darwinian bent.[193] Thus, there is much in favor of the view that Jerne's natural selection theory and Burnet's subsequent clonal selection theory should, at least in part, be seen in the light of the neo-Darwinian synthesis of the 1940s and 1950s. In fact, the three generations of theories of antibody formation are correlated in time with three generations of general evolutionary theories: Ehrlich's side-chain theory from the turn of the century was proposed within the framework of nineteenth-century Darwinian selectionist ideas; the template

193. Burnet, *Changing Patterns* (above, n. 19).

theories of the 1930s coincided with the decline of Darwinism and the corresponding popularity of neo-Lamarckism;[194] and finally, the revival of the selectionist idea in immunology in the 1950s followed in the wake of the neo-Darwinian synthesis.[195]

I have emphasized the significance of the phage group, and the implicit and explicit Darwinian ideas floating around in phage circles at the time, as an important context for understanding the origin of the selection theory of antibody formation. This emphasis should not overshadow the existence of other cultural, intellectual, and personal circumstances. For example, Jerne's assertion that his very personal reading of Kierkegaard played a major role in the "train of thought" leading to the selection theory remains to be investigated, as well as the significance of other literary and philosophical ideas for his intellectual outlook. A full reconstruction of the origin of the central dogma in contemporary immunology should also bring these literary, philosophical, and personal contexts to the fore.

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194. For a general treatise on the decline of Darwinist thinking, see Peter J. Bowler, *The Eclipse of Darwinism: Anti-Darwinian Evolution Theories in the Decades Around 1900* (Baltimore: Johns Hopkins University Press, 1983).

195. The parallel between the first two waves of theories of antibody formation and general evolutionary thought has also been hinted at by Silverstein: the first theory of immunity advanced by Metchnikoff "followed strict Darwinian evolutionary principles, and the first theory of antibody formation proposed by Paul Ehrlich . . . was similarly based. . . . [whereas] the new chemical [instruction] theories of antibody formation were quite Lamarckian in nature" (Silverstein, "Dynamics of Conceptual Change" [above, n. 24], pp. 523–524). Silverstein does not follow up the parallel with the neo-Darwinian synthesis, however.

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