Respectfully,
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From pneumonia to DNA: The research career of Oswald T. Avery

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> Medical science?...That is a contradiction in terms. There is no such thing. You should begin with the chemistry of proteins, as I do.[1]

IT IS COMMONPLACE to assert that the marriage of science and medicine has resulted in changes in medical knowledge and practice, medical education, organization of medical care, and the social status of medicine and its practitioners. But while science is no longer seen exclusively as an engine of technical progress in medicine,[2] and the various meanings of science in medicine have been explored by historians and sociologists,[3] the complementary process of incorporating medical concerns in laboratory research has been treated as relatively

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The following abbreviations are used: *BHM, Bulletin of the history of medicine*; *BMNAS*, National Academy of Sciences, *Biographical memoirs*; *JHB, Journal of the history of biology*; *JEM, Journal of experimental medicine*; *RBSD*, Board of Scientific Directors of the Rockefeller Institute for Medical Research, *Reports, Rockefeller University Archive; RC, Reports to the Corporation of the Rockefeller Institute of Medical Research*, Rockefeller University Archive;

1. Jacques Loeb, quoted in René J. Dubos, *The professor, the institute, and DNA* (New York, 1976), 42.

2. Erwin Ackerknecht, *Short history of medicine* (New York, 1955), and William Rothstein, *American physicians in the nineteenth century: From sects to science* (Baltimore, 1972).

3. John H. Warner, "Science in medicine," in Sally Gregory Kohlstedt and Margaret W. Rossiter, eds., *Historical writing on American science. Perspectives and prospects* (Baltimore, 1985); Gerald L. Geison, "'Divided we stand:' Physiologists and clinicians in the American context," in Morris J. Vogel and Charles E. Rosenberg, eds., *The therapeutic revolution. Essays in the social history of American medicine* (Philadelphia, 1979), 67–90; S.E.D. Shortt, "Physicians, science and status: Issues in the professionalization of Anglo-American medicine in the nineteenth century," *Medical history, 27* (1983), 51–68; Barbara G. Rosenkrantz, "Cart before horse: Theory, practice, and professional image in American public health, 1870–1920," *Journal of the history of medicine, 29* (1974), 55–73; Howard S. Berliner, *A system of scientific medicine. Philanthropic foundations in the Flexner era* (New York, 1985); Rosemary Stevens, *American medicine and the public interest* (New Haven, 1971).

straightforward and unproblematic. Historians of the biomedical sciences rely on terms such as "medical orientation" or "clinical interest" in order to describe the role of medical concerns in the development of biochemistry, bacteriology or physiology in the prewar period.[4] They have pointed out that biomedical scientists relied on the (putative) medical relevance of their research in order to legitimize their fields, to procure institutional support and funding.

What does it mean to say that research performed in the laboratory is medically oriented? How are medical problems transformed before they become subjects of research in a laboratory, and how do they shape the research process itself? What role do they play in the formulation of research problems, in experimental practices, in the development of research lines, in the presentation of research results? The answers to such questions are important to an understanding of how practical concerns can be incorporated into scientific research and shape its development.

This paper assumes that when scientists formulate the problems they wish to address, choose approaches and methods, and interpret and present their results, they do so within specific evidential contexts. Within these contexts experiments as well as their results become meaningful knowledge claims. Whether these contexts are understood as classificatory schemes, more or less formal theories, laws, hypotheses, networks of concepts, productive metaphors, or interpretative schemes, knowledge claims are considered as legitimate contributions to science only when interpreted within such contexts.[5] A variety of distinct evidential contexts is available within every field; some of them are relatively independent, whereas others are linked together so that a claim made within one context can also be made significant in another.

4. Robert E. Kohler, "Medical reform and biomedical science: Biochemistry—A case study," in Vogel and Rosenberg (ref. 3), 27–66, and *From medical chemistry to biochemistry. The making of a biomedical discipline* (Cambridge, 1982); Geison (ref. 3); Russel C. Maulitz, "'Physician versus bacteriologist:' The ideology of science in clinical medicine," in Vogel and Rosenberg (ref. 3), 91–107; Ilana Löwy, "Biomedical research and the constraints of medical practice: James Baumgardner Murphy and the early discovery of the role of lymphocytes in immune reactions," *BHM, 63* (1989), 356–391, and "The impact of medical practice on biomedical research: The case of human leucocyte antigen studies," *Minerva, 23* (1989), 171–200; Gerald L. Geison, ed., *Physiology in the American context, 1850–1940* (Bethesda, MD, 1987); Philip J. Pauly, "The appearance of academic biology in late nineteenth century America," *Journal of the history of biology, 17* (1984), 369–397; Olga Amsterdamska, "Medical and biological constraints: Early research on variation in bacteriology," *Social studies of science, 17* (1987), 657–87.

5. Trevor J. Pinch, "Towards an analysis of scientific observation: The externality and evidential significance of observational reports in physics," *Social studies of science, 15* (1985), 3–36.

A series of arguments and reinterpretations (call them "translations") is required before a claim meaningful within one evidential context can be made significant in another. Similarly, before a practical concern can become a subject of scientific research, it has to be placed within a particular evidential context. Accordingly, in order to describe the role that medical problems play in biomedical research, I attempt to reconstruct the various changing chains of translations through which one particular biomedical scientist linked his own investigations to a number of distinct evidential contexts, and I examine how these different contexts related to the medical problem he was ostensibly addressing. In order to gain a better understanding of the choice of particular evidential contexts and translations at different times, I examine not only the available cognitive opportunities and constraints, but also changes in the social and institutional setting in which research took place: access to particular research materials, instrumentation, expertise, the expectations and preferences of the governing bodies of the institute, and the reigning ideology of scientific medicine.

The interpretation of laboratory activities within distinct evidential contexts takes place both in the laboratory and in the various other settings—behind writing desks, at conferences, in informal conversations—in which scientists consider their research. As different kinds of scientific texts can be addressed to different audiences, so discussions in the laboratory can concern experiments planned for the following week or month or year, or deal only with difficulties in interpreting a single experimental run; the relevant evidential contexts shift and change, along with the observed links to practical medical concerns. Our answer to the question of how medical concerns affect the research practices of biomedical scientists might differ depending on whether we reconstruct these research practices by examining day-to-day research activities, research papers published in scientific journals, formal reports to sponsors and research proposals, or long-term research interests and approaches. I examine the significance of such differences by asking about their character and their sources: how are the evidential contexts invoked in day-to-day research different from those that prevail when the research is presented in scientific articles or in reports to the governing bodies of the institution in which the researcher worked? How are the different invoked contexts related to one another? Are there systematic differences in the manner in which practical concerns appear to be incorporated into research practices, depending on whether we look at long-term reconstructions of research activity or at short-term reports in individual scientific papers?

The research career of Oswald T. Avery provides a unique opportunity to examine the ways in which a single medical problem can be addressed in research over a long period of time. Some information about the day-to-day activities in his laboratory are available in written recollections of the participants; unfortunately, the laboratory notebooks have not survived. Besides these recollections and other biographical materials, the reconstructions presented here draw on an analysis of Avery's papers and on the very detailed reports he submitted several times a year to the Board of Scientific Directors and to the Corporation of the Rockefeller Institute.

1. O.T. AVERY: MEDICAL SCIENTIST OR (PROTO) MOLECULAR BIOLOGIST?

When in 1913 Oswald T. Avery came to work at the Rockefeller Institute Hospital he joined a group of clinical researchers attempting to develop a better treatment for lobar pneumonia. Avery spent almost all of the following thirty-five years at the Rockefeller investigating the pneumococcus, and, as his one-time collaborator, Collin MacLeod emphasized: "it is well to remember that Dr. Avery was interested primarily in disease—in pneumococcal pneumonia and the bacterium that causes it, pneumococcus—and that his whole scientific life was devoted to understanding the disease, how pneumococcus is able to exert its pathogenicity, the immune responses to it, how recovery takes place and how one can intervene."[6]

Today, however, Avery is remembered not for his contributions to the medical understanding, diagnosis or treatment of pneumonia, but for a paper in which, together with Collin MacLeod and Maclyn McCarty, he identified desoxyribonucleic acid as the substance responsible for specific hereditary transformations of the pneumococcus.[7] For some, this chemical identification of the substance that induced specific hereditary changes in a microorganism amounted to the identification of DNA as the genetic material of the cell. Accordingly, they see Avery's discovery as one of the turning points in the development of molecular biology. According to Frank MacFarlane Burnet, who visited the Rockefeller Institute during the war, "in retrospect, the discovery that DNA could transfer genetic information from one

6. Collin MacLeod speaking at the dedication of Avery Gateway, 29 Sept 1965, transcribed text, René Dubos papers, 42:5, RUA.

7. Oswald T. Avery, Collin MacLeod, and Maclyn McCarty, "Studies on the chemical nature of the substance inducing transformation of pneumococcal types. Induction of transformation by desoxyribonucleic acid fraction isolated from pneumococcus type III," *JEM*, *79* (1944), 137–157.

type of pneumococcus to another almost brought the end of one field of scholarly investigation, medical bacteriology, and heralded the opening of molecular biology which has dominated scholarly thought in biology ever since." Burnet esteemed Avery's discovery as the source of a major disciplinary reorientation, which "swung microbiology perhaps forever from a primary desire to prevent and cure infectious diseases to its current preoccupation with molecular biology."[8]

To historians of molecular biology, the role of Avery's identification of DNA as the chemical substance responsible for pneumococcal type transformations is far more complex and generally less decisive. Some point to the fact that it stimulated other research on DNA in biochemistry and bacterial genetics,[9] while others not only identify other, independent research groups as central in the transition to molecular biology,[10] but also argue that many geneticists and biochemists were slow to accept Avery's discovery and its implications.[11]

It is puzzling that the discovery that Burnet rated a turning point from medical microbiology to molecular biology was made by men trained in medicine and working in a research hospital, in a department concerned with respiratory diseases. The puzzle becomes more

8. Frank McFarlane Burnet, *Changing patterns: An atypical autobiography* (London, 1968), 81, 59.

9. Erwin Chargaff, *The Heraclitean fire: Sketches from a life before nature* (New York, 1978); Franklin H. Portugal and Jack S. Cohen, *A century of DNA: A history of the discovery of the structure and function of the genetic substance* (Cambridge, 1977), 198–200; Joshua Lederberg, "Forty years of genetic recombination in bacteria," *Nature, 324* (1986), 627–628.

10. Robert Olby "Avery in retrospect," *Nature, 239* (1972), 295–96, and *The path to the double helix* (London, 1974); Horace F. Judson, *The eighth day of creation: The makers of the revolution in biology* (New York, 1979); Lily Kay, "Conceptual models and analytical tools: The biology of the physicist Max Delbrück," *JHB, 18* (1985), 207–246, *Cooperative individualism and the growth of molecular biology at the California Institute of Technology, 1928–1953* (Ph.D. thesis, Johns Hopkins University, Baltimore, 1986), and "Selling pure science in wartime: The biochemical genetics of G.W. Beadle," *JHB, 22* (1989), 73–101; Pnina Abir-Am, "The biotheoretical gathering, transdisciplinary authority and the incipient legitimation of molecular biology in the 1930s: New perspective on the historical sociology of science," *History of science, 25* (1987), 1–70, "How scientists view their heroes: Some remarks on the mechanism of myth construction," *JHB, 15* (1982), 281–315, "Themes, genres and orders of legitimation in the consolidation of new disciplines: Deconstructing the historiography of molecular biology," *History of science, 23* (1985), 73–117, and "Noblesse oblige: Lives of molecular biologists," *Isis, 82* (1991), 326–343; Ilana Löwy, "Variances in meaning in discovery accounts: The case of contemporary biology," *HSPS, 21:1* (1990), 87–121.

11. H.V. Wyatt, "When does information become knowledge?" *Nature, 235* (1972), 86–89; Joshua Lederberg, "Reply to H.V. Wyatt," *Nature, 239* (1972), 234; Olby (ref. 10); Gunther S. Stent, "Prematurity and uniqueness in scientific discovery," *Scientific American, 227* (1972), 84–93, where Avery's case is cited as an example of prematurity.

striking when, instead of looking at Avery's work on pneumococcal transformation in isolation, we examine his entire research path. In addition to the discovery of the function of DNA in bacterial transformations, Avery contributed to the understanding of biological and immunological specificity; and, although finding an effective therapy for pneumonia was the rationale for the entirety of Avery's research program, "his discoveries had only few and limited applications of immediate practical importance. His contributions were to the understanding of biological phenomena, and have influenced the practice of medicine only in an indirect manner."[12] How did research oriented to the solution of a specific medical problem—research focused on a single disease, its causation by a specific microorganism and the immune reactions to it—lead primarily to major biological discoveries? How did Avery's focus on pneumonia affect his research program? In what respects did the medical concerns figure in Avery's overall research?

2. THE INITIAL TRANSLATION: PNEUMONIA AT THE ROCKEFELLER INSTITUTE

What counts as a medical problem changes historically and culturally, and can be a matter of debate among different professional and lay groups. According to Charles E. Rosenberg, "Disease is at once a biological event, a generation-specific repertoire of verbal constructs reflecting medicine's intellectual and institutional history, an aspect of potential legitimation for public policy, a potentially defining element of social role, a sanction for cultural norms, and a structuring element in doctor-patient interactions. In some ways disease does not exist until we have agreed that it does—by perceiving, naming, and responding to it," and, we might add, since the mid-19th century, by making it a subject of scientific research. One of the processes accompanying the scientification of medicine has been the medicalization of social problems; as more problems seem amenable to medical intervention, so also more problems become legitimate subjects of biomedical research.[13] Biomedical scientists who focus their research on a particular medical problem are facing a scientifically and clinically prestructured reality. This prestructuring does not, however, mean that at a specific time and place a medical problem will be defined unambiguously in the clinic or that its various aspects will be seen as forming a coherent unity. Definitions of diseases, their classifications, significant features, and importance may vary among different clinical

12. Dubos (ref. 1), 89.

13. C.E. Rosenberg, "Disease in history: Frames and framers," *The Milbank quarterly, 67*, suppl. 1 (1989), 1–15, on 1–2.

specialties, and preclinical biomedical scientists of different disciplinary backgrounds are likely to assign different meanings and status to these differing conceptions.

Biomedical scientists wishing to address medically relevant issues in their laboratory thus have to redefine unwieldy, complex, multifaceted, and varying clinical phenomena (or representations of such phenomena made by practicing physicians) into researchable—and scientifically legitimate—questions subject to examination by the available laboratory methods. In a specific laboratory setting, these redefinitions are also shaped by the local institutional culture, the availability of specific instruments or expertise, the possibility of using particular experimental models, and access to patients and other research materials. A commitment to a particular translation enables scientists to pursue the solution of a medical problem by engaging in research within some conceptual and instrumental, that is, evidential context.

When the hospital of the Rockefeller Institute chose to focus research on pneumonia, it was a common and serious, often fatal disease. In the early 1900s in the United States, pneumonia, as the leading cause of death, accounted for 202 deaths per 100,000 population.[14] Although it was recognized in the 1880s as a bacterial disease, the characterization of its major etiological agent, the pneumococcus, did not result in the total identification of the disease with the responsible bacterium. Although bacteriologists isolated the pneumococcus from a majority of cases, they also believed that other bacteria (e.g., the streptococcus or Friedländer's bacillus) were sometimes involved. Also, lobar pneumonia was not usually contagious: despite occasional epidemics, particularly in institutions, researchers and physicians agreed that contact with the bacterium was not sufficient to produce the disease. Pneumonia often followed some other illness; it seemed to be particularly prevalent among certain groups, in certain seasons, and dependent on the general state of health of the victim. Moreover, the pneumococcus often turned up in the mouths of healthy individuals. Factors other than the bacterium appeared to play an important role

14. Harry F. Dowling, *Fighting infection. Conquests of the twentieth century* (Cambridge, 1977), 230. Cf. Rufus Cole's observation of the high mortality rates from pneumonia in New York: "the number of deaths in New York, due to pneumonia caused by pneumococci of Type I, is greater than the deaths due to diphtheria, and much greater than the total number of deaths due to scarlet fever, cerebro-spinal fever, and typhoid fever combined" (*RBSD*, 3:IV, 23–24, report of Jan 1915); "in 1915 probably 1800 deaths in New York City were due to Acute Lobar Pneumonia of Type I alone. This is as many as all the deaths from typhoid fever, measles, scarlet fever, whooping cough and cerebro-spinal meningitis combined, and almost as many as all the deaths occurring in the present epidemic of poliomyelitis" (*RC*, 1915/16, 3:IV, 36, report of Oct 1916).

in the disease. Since pneumonia could be diagnosed readily in the clinic without a bacteriological examination, the bacterial etiology of the disease was not the foremost concern for the clinicians who regularly resorted to an "expectant treatment" and used a variety of methods to alleviate the symptoms.[15] As Michael Worboys reminds us, "for clinicians pneumonia was more an illness of a certain kind of person than a specific disease entity."[16]

If for the clinicians the bacterial causes of pneumonia were of secondary importance, this cannot be said of the research conducted at the Rockefeller Institute for Medical Research or at the hospital, where research on pneumonia relied almost exclusively on the bacteriological definition of the disease. A number of institutional and intellectual circumstances contributed to the adoption of this definition.

From its inception, the Rockefeller Institute focused much of its attention on bacteriology. All members of the Institute's original board of directors were trained in pathology and interested in infectious diseases.[17] When the hospital of the Institute opened in 1910, three out of the five diseases on which research in the hospital was to focus were infectious (pneumonia, syphilis, and poliomyelitis), and investigations of various other infectious diseases were undertaken throughout the interwar years. Given the hope generated by the discoveries of the etiology of many infectious diseases and the development of specific treatments for diseases like diphtheria and rabies, as well as the improvements in surgical techniques based on antisepsis and asepsis during the last quarter of the 19th century, infectious diseases appeared at the beginning of the 1900s as the most promising subjects for scientific medical research. The major medical research institutes established at that time—the Lister Institute in London, the Pasteur Institutes, and Koch's Institute in Berlin—all emphasized the central importance of bacteriology. To some extent, these institutes served as models for the Rockefeller.

Bacteriological research also fitted well with the ideology of laboratory medicine advocated at the Rockefeller Institute Hospital, and

15. In his *The principles and practice of medicine* of 1892 and in later editions, Osler characterized pneumonia as "a self-limited disease [that] runs its course uninfluenced in any way by medicine." Cf. Peter C. English, "Therapeutic strategies to combat pneumococcal disease: Repeated failure to adopt pneumococcal vaccine," *Perspectives in biology and medicine, 30* (1987), 170–185.

16. Michael Worboys, "Treatments for pneumonia in Britain, 1910–1940," in I. Löwy, O. Amsterdamska, J. Pickstone, and P. Pinnell, eds., *Medicine and change: Historical and sociological studies of medical innovation* (Paris, 1993), 317–336.

17. George W. Corner, *The history of the Rockefeller Institute, 1901–1953. Origins and growth* (New York, 1964), 36.

with the organization of the hospital as both a clinic and a research center. Rufus Cole, the first Director of the hospital, who had come to the Rockefeller from the biological laboratory at Johns Hopkins Hospital, was strongly influenced by Lewellys F. Barker's vision of the hospital laboratory as a place for original research, and not only routine diagnostic work. In his plans for the hospital, Cole tried to insure that every physician working there would also be involved in research, including laboratory research.[18] The facilities available included not only well equipped bacteriological laboratories, but also facilities for animal research. In addition, the availability of animal models (mice, rabbits, dogs, and monkeys) for the investigation of pneumonia allowed for a smooth transition from clinical to experimental research.

Cole gave pneumonia research at the Rockefeller its dominant direction. Most of his research before he came to the Rockefeller focused on typhoid, but he had also published on pneumonia, which he chose for his own studies at the Hospital. During the first several years at the Rockefeller Hospital, working together with Alfonse Dochez and Henry Marks, Cole identified distinct strains of the pneumococci and applied this classification to the development of the serum treatment. By 1912, they had prepared a serum for pneumonia caused by Type I pneumococci and were working on sera for the other strains.[19] When Cole hired Avery in 1913, it was with the understanding that Avery would join these bacteriological and immunological investigations of the pneumococcus and work on the development of more effective serum treatment for pneumonia.[20]

Cole's choice to define pneumonia by its major etiological agent and to define his problem as one of finding a therapy, preferably a serum, was not the only possible one. Even a strictly bacteriological definition of the disease did not necessarily dictate research directed to the development or improvement of a serum therapy. A number of British and South African bacteriologists were working at that time on the development of a preventive vaccine for pneumonia.[21] Although Gay and Chickering did some research on vaccines at the Rockefeller

18. C. Phillip Miller, "Rufus Cole," *BMNAS, 50* (1979), 119–139; Corner (ibid.), 91–94.

19. Rufus Cole, "Blood cultures in pneumonia," *Johns Hopkins Hospital Bulletin, 13* (1902), 136; "Pneumococcus septicemia, meningitis and arthritis," ibid., 143; Corner (ref. 17), 99–101; Rufus Cole, "Pneumococcus infection and immunity," *JAMA, 59* (1912), 693, and "Treatment of pneumonia by specific serums," ibid., *61* (1913), 663; Rufus Cole and Alphonse R. Dochez, "Report of studies on pneumonia," Association of American Physicians, *Transactions, 28* (1913), 606–616.

20. Alphonse R. Dochez, "Oswald Theodore Avery," *BMNAS, 32* (1958), 31–49; Dubos (ref. 1), 62–63.

21. English (ref. 15).

Hospital before World War I and Chickering and Austin worked on it during the war, their work was incidental to the effort to develop effective sera.[22] A few non-bacteriological approaches to therapy were also attempted: examination of pathological changes accompanying pneumonia, investigation of the epidemiology of the disease and of its spread, the use of chemotherapeutic agents (such as optochin and, much later, sulfapyridine) developed elsewhere, and alleviation of the disease's symptoms (e.g., the oxygen chamber). With the possible exception of the epidemiological research conducted by Stillman, which, however, also had a bacteriological bent and involved animal experimentation, no one pursued these other approaches as systematically or intensively as Avery did his own.

Cole's and Avery's redefinitions of the problem of pneumonia as one of understanding the biological properties of the pneumococcus and of immune reactions to it must be regarded as only one of the possible translations of the medical problem into a laboratory one. Their choices were shaped not only by the clinical understanding of pneumonia and the bacteriological knowledge of the time, but also by the background of the researchers involved and the local institutional conditions at the Rockefeller: the emphasis on bacteriological research and the place of this type of research in the prevailing view of what scientific medicine should be, the facilities available, the emphasis on combining clinical and laboratory research, and the instrumental opportunities provided by the possibility of infecting animals.

Practice comes first: The pre-war years

Cole's success in typing the pneumococci and in developing a serum for pneumonia caused by Type I provided Avery with the initial translations he relied on: to enhance the affected organism's ability to destroy the offending organism by supplying serum appropriate to the type of pneumococcus present. The development and use of specific sera required proper typing of the offending organisms, rapid diagnostic methods, efficient serum production in horses, standardization of the serum and its dosage, and improvement of serum quality.

Accepting this basic formulation, Avery initially turned his attention to practical difficulties encountered in the hospital. Since serum sickness often complicated serum therapy, Avery worked on improving sera through purification and greater concentration of the active fractions so that the "antibacterial potency might be conserved with a

22. "Report by Dr. Gay," *RBSD*, Jan 1915, 3:IV; *RBSD*, Jan and Apr 1918, 3:VI; *RC*, Oct 1918, 3:VI.

minimum of foreign protein."[23] The use of the serum in treatment also required standardization of its potency, and in 1916 Avery devoted time to the development of the methods necessary for standardization.[24] When some atypical strains of pneumococcus were identified in the Johns Hopkins Hospital at Baltimore, Avery became involved in their typing;[25] and when serum for Type III became available, Avery tested whether all Type III pneumococci are immunologically the same.[26] According to Dubos, during this period Avery was also in charge of producing the various sera, testing their effectiveness on animals, and running the diagnostic tests required before the administration of the appropriate serum to the patient.[27]

Avery's attention to the daily practical problems in the Hospital appears also in his early papers, which provide ample discussions of the medical relevance of the problems and often rely on evidence directly from the clinic. For example, examining certain atypical pneumococcus organisms that agglutinated with delay in Type II antiserum, Avery motivated his interest in these deviant types by referring to the confusion they could cause in diagnosing pneumonia through agglutination (typing through agglutination was the first step in the administration of appropriate serum).[28] Similarly, when he and Dochez studied the types of pneumococcus present in the mouths of healthy and sick individuals, he was interested in whether "infection with pneumonia takes place either by contact with infected individuals or apparently healthy carriers."[29]

At this stage of Avery's research, translations from the clinical problems, addressed to research presented in articles or reported to the Board of Scientific Directors, were explicitly stated and relatively direct. But the attention to specific and often limited problems encountered in the serum treatment of pneumonia at the Hospital resulted also in a lack of a coherent, longer-term research strategy. Continuity seems to have been provided by the clinical practice in the hospital, which regularly treated pneumonia patients, rather than by research results leading to further questions or problems. Throughout

23. Oswald T. Avery, "The distribution of the immune bodies occurring in antipneumococcus serum," *JEM, 21* (1915), 133–145; see also *RBSD*, Jan, Apr and June 1915, Jan, Apr and June 1916, 3:IV.

24. *RBSD*, Jan 1917, 3:V, 64–65.

25. Oswald T. Avery, "A further study on the biologic classification of pneumococci," *JEM, 22* (1915), 804–819.

26. *RC*, Oct 1916, 3:IV, 360–361; *RBSD*, Apr 1916, 3:IV, 246–248.

27. Dubos (ref. 1), 91.

28. Ref. 26.

29. Alfonse Dochez and Oswald T. Avery, "Varieties of pneumococcus and their relation to lobar pneumonia," *JEM, 21* (1915), 114–132, on 115.

the pre-war period Avery worked simultaneously on several different and unrelated problems.

During these early years at the Hospital, Avery occasionally addressed issues not obviously applicable to clinical practice. Reports on the work conducted at the Hospital during that period made a distinction between research aiming at the solution of concrete practical problems and research having "theoretical importance" but no immediate utility in the clinic. The *Report* to the Corporation for 1916, for example, ended with a list of "other studies concerning pneumonia and the pneumococcus infections...which however, at present have theoretical rather than practical interest."[30] Similarly, in 1917, some of the work conducted by Dochez, Blake, Palmer, and Avery was described as having "much theoretical interest, but...not [being] at present applicable to the practical problem relating to this disease."[31]

Some of Avery's pre-war research was placed in this relatively marginal category, "theoretically but not practically relevant." For example:[32]

> The pneumonia studies also have yielded other results which are at present of *only theoretical importance*, though it is hoped to make practical application of certain of them. In the investigation of the mode of action of the immune serum, for instance, Dr. Dochez and Dr. Avery have shown that the immune serum has a depressing action on the metabolic activities of bacteria. This is one of the actions of the immune serum which has been little studied, but which may be of considerable importance. They have named this form of activity "antiblastic."

Although in studying "antiblastic immunity" Avery and Dochez defined the problem of treating pneumonia as one of administering the appropriate serum, the question addressed here did not stem directly from the clinic but constituted instead a further extension of translating the treatment of pneumonia into producing an immune serum. In asking how immune serum affects the bacterium, Avery and

30. *RC* (ref. 26), 364.

31. *RC*, Oct 1917, 3:V, 266. This distinction was drawn especially in the *Reports* to the Corporation, which, being addressed to non-scientists, tended to emphasize the practical relevance of the results obtained in the hospital and its laboratories, and downplay work only "scientifically" relevant. But the category of "theoretical rather than practical relevance" also appears occasionally in the prewar period in the *Reports* to the Board of Scientific Directors (e.g., *RBSD*, Apr 1915, 3:IV, 70). After World War I, the category was seldom used.

32. *RC*, Oct 1915, 3:IV, 149. Similar qualifications were added to the reports on Avery's research on the growth of pneumococci in dilute solutions of bile and on their action on hemoglobin.

Dochez did not speculate about how an answer to this question might be relevant to the clinical problem of treatment (or diagnosis or prognosis) of pneumonia. They formulated no hypotheses that allowed for a linkage back from the laboratory to the clinic. Thus, while the initial definition of the situation incorporated medical issues and concerns, the lack of specification of how better knowledge of serum action was to contribute to the solution of any particular clinical problem loosened the relation between research and clinical practice. Research questions that incorporate medical problematics do not necessarily have practical medical implications that can be articulated explicitly.

In addition to investigating the mode of activity of the serum, Dochez and Avery asked "why it should be possible to produce an effective serum against pneumococci of Type I and only one of much less value against pneumococci of Type II, and one of very slight value against pneumococci of Type III?" This question, which reflected the state of the therapeutic practice at the time, was linked with the hypothesis that the relative differences in the effectiveness of the serum related to "capsules" possessed by organisms of different types. Dochez undertook the determination of "the nature of the capsular substance, and its relative antigenic activity."[33] This translation of the serum problem into the problem of capsules and their antigenic activity played an important role in Avery's future research. Initially, however, no sooner was the question posed than another replaced it.

The initial course of the research on capsules provides a revealing example of the primacy of clinical concerns at the hospital before World War I, and of the mode in which "practical" and "theoretical" studies were separated within the Institute. In the course of his research on capsules, Dochez found that cell-free filtrates of pneumococcus cultures contained a substance that precipitated with specific immune sera and that the pneumococcus elaborated during its periods of growth. The antigenic specificity of the isolated substance and the determination that it was elaborated during the growth of bacteria suggested that it might play a role in the immune reactions under study by Dochez and Avery. What attracted their immediate attention, however, was not this "theoretical" promise, but the possibilities of applying their finding in the clinic as a basis for a better diagnostic technique. Accordingly, they tested for the presence of this substance in the blood and urine of patients with pneumonia. On discovering it in a substantial proportion of cases, they attempted to find a correlation between "its appearance and disappearance...[and] the clinical course of the disease, its relation to prognosis and its significance in

33. *RC*, Oct 1916, 3:IV, 361.

facilitating early diagnosis."[34] At the same time, first attempts were made to identify the substance chemically and to study its role in the intoxication accompanying pneumonia, thus placing the research within the evidential context of toxicity of bacteria.[35]

As this work progressed, the identification of the substance with the capsular material temporarily disappeared and the initial problem of understanding differences between the efficacy of different sera also temporarily receded into the background. The possible relevance of the substance for diagnostic purposes promised a more direct return from the laboratory to the clinic and suggested a different set of questions. For the purposes of diagnosis, Avery and Dochez were interested in the time when the substance appeared in the blood and urine, in the reliability with which it could be detected, and in its role during the course of the disease. The temporary redefinition of the clinical problem at hand as one of diagnosis and prognosis rather than one of the therapeutic efficacy of the different sera privileged the more immediate, "practically relevant" evidential contexts over the more elaborate, "theoretically interesting" ones, in which the efficacy of the serum was linked to the nature of the pneumococcus capsule. Throughout this period, translations that allowed for a more direct return from the laboratory to the clinic were chosen systematically.

Wartime disruption

The involvement of the United States in the first world war changed the relationship between the hospital of the Rockefeller Institute and its environment. Not only did a number of physicians and researchers enter military service or leave the hospital to take up temporary duties elsewhere, but even the remaining staff members became engaged in the training of army medical officers and in investigations of epidemics of respiratory tract diseases in army camps and hospitals.[36] The hospital, which previously had taken only referred patients suffering from a small number of selected diseases, had to accept a larger number of patients, many of them soldiers, who were not carefully screened or selected. There were times when respiratory diseases (pneumonia in particular) had the hospital's exclusive attention.[37] At

34. *RBSD*, Jan 1917, 3:V, 65–66.

35. Alfonse R. Dochez and Oswald T. Avery, "The elaboration of specific soluble substance by pneumococcus during growth," *JEM, 27* (1917), 477–493.

36. Corner (ref. 17), 138–141; *RC*, Oct 1918, 3:VI, 326–332.

37. *RC* (ref. 36), 329: "During the past year, the facilities of the hospital wards have been employed almost entirely in the care of patients suffering from pneumonia and of those suffering from syphilis. A large number of patients treated have been soldiers sent from nearby camps."

the same time, the hospital ceased to be the main setting in which the Rockefeller clinical researchers conducted their investigations. Both Dochez and Avery investigated pneumonia epidemics in army camps.[38]

Though this work involved much routine (determining types of bacteria involved, introducing the use of serum treatment, studying the mode of transmission, etc.), an encounter with an atypical form of pneumonia caused by the streptococcus led to investigations of this bacterium, which also continued briefly after the war.[39] The model followed the earlier pneumococcus studies, with much attention devoted to the classification of different types in terms of their immunological characteristics. The pressure of external circumstances also led to investigations of the influenza epidemic in 1918 and 1919, specifically of the involvement of *b. influenzae*.[40] This was the only time during Avery's long tenure at the Rockefeller when he diverted his attention from the pneumococcus.

Changes in the nature of clinical practice during the war thus had an immediate though short-term impact on the direction of Avery's, Cole's, and Dochez' investigations. At the hospital itself, immediate practical problems with diagnosis, its routinization, and the standardization of the serum took over, while the prevalence of particular types of respiratory disease in the army and the civilian population dictated an interest in respiratory illnesses caused by bacteria other than the pneumococcus.

Science comes first

Avery returned to the pneumococcus almost as soon as the war and the influenza epidemic ended. By 1919, he was investigating optimum growth conditions for pneumococcus; a year later, he was engaged in studies of pneumococcal enzymes.[41] The full-time return to

38. *RBSD*, Apr 1918, 3:VI, 213–214; *RC* (ref. 36), 330–335.

39. Oswald T. Avery and Glenn E. Cullen, "The use of final hydrogen ion concentration in differentiation of streptococcus haemolyticus of human and bovine types," *JEM, 29* (1919), 215–234; Alfonse Dochez, Oswald T. Avery, and Rebecca C. Lancefield, "Studies on the biology of streptococcus. I. Antigenic relationships between strains of streptococcus haemolyticus," *JEM, 30* (1919), 179–213; and Oswald T. Avery, Alfonse Dochez and Rebecca C. Lancefield, "Bacteriology of streptococcus hemolyticus," *Annals of otology, rhinology and laryngology, 28* (1919), 350–360.

40. *RBSD*, Jan 1919, 3:VII, 57–64. "We have, therefore, been compelled by circumstances to extend our study of acute lobar pneumonia to the study of influenza." Avery, "A selective medium for B. influenzae. Oleate-hemoglobin agar," *JAMA, 71* (1918), 2050.

41. *RBSD*, Jun 1919, 3:VII, 178–79; *RBSD*, Apr 1920, 3:VIII, 101–105; *RC*, Oct 1920, 3:VIII, 246–248.

the pneumococcus did not mean a return to the previous translations: this time Avery did not begin by isolating an aspect of some specific clinical problem associated with pneumonia or its treatment, and then translating it, step by step, into a research problem amenable to laboratory investigation. The studies with Glen Cullen on growth conditon, and later those with Hugh Morgan, Theodor Thjötta, and James Neill, focused on the biological (biochemical) properties of the pneumococcus: nutritional requirements, metabolism, and so on;[42] but without specification of the link between the knowledge of these properties and either the understanding or the management of pneumonia in the clinic. Insofar as the papers on metabolism and nutrition and the research reports from this period make any references to medical interests or justify research in terms of its clinical relevance, they do so by appealing to the importance of a general knowledge of the biology of the bacteria for an understanding of the diseases they cause.

One of the first articles in this group of papers, for example, asserts:[43]

42. K.G. Dernby and Oswald T. Avery, "The optimum hydrogen ion concentration for the growth of pneumococcus," *JEM, 28* (1918), 345–357; Avery and Cullen, "The use of final hydrogen ion concentration in differentiation of streptococcus haemolyticus of human and bovine types," *JEM, 29* (1919), 215–234, "Hydrogen ion concentration of cultures of pneumococci of the different types in carbohydrate media," *JEM, 30* (1919), 359–378, "Studies on the enzymes of pneumococcus. I. Proteolytic enzymes," *JEM, 32* (1920), 547–569, "II. Lipolytic enzymes: esterase," *JEM, 32* (1920), 571–582, "III. Carbohydrate splitting enzymes: invertase, amylase, and inulase," *JEM, 32* (1920), 583–593, "IV. Bacteriolytic enzyme," *JEM, 39* (1923), 199–205; Morgan and Avery, "Studies on bacterial nutrition. IV. Effect of plant tissue upon growth of pneumococcus and streptococcus," *JEM, 38* (1923), 207–217; Avery and Morgan, "The occurrence of peroxide in cultures of pneumococcus," *JEM, 39* (1924), 275–287, "V. The effect of plant tissue upon the growth of anaerobic bacilli," *JEM, 39* (1924), 289–302; Thjötta and Avery, "II. Growth accessory substances in the cultivation of hemophilaic bacilli," *JEM, 34* (1921), 97–114; "III. Plant tissue as a source of growth accessory substances in the cultivation of bacillus influenzae," *JEM, 34* (1921), 455–466; Avery and Neill, "Studies on oxidation and reduction by pneumococcus. I. Production of peroxide by anaerobic cultures of pneumococcus on exposure to air under conditions not permitting active growth," *JEM, 39* (1924), 347–355, "II. The production of peroxide by sterile extract of pneumococcus," *JEM, 39* (1924), 357–366, "III. Reduction of methylene blue by sterile extracts of pneumococcus," *JEM, 39* (1924), 543–552, "IV. Oxidation of hemotoxin in sterile extracts of pneumococcus," *JEM, 39* (1924), 745–755, Neill and Avery, "V. The destruction of oxyhemoglobin by sterile extracts of pneumococcus," *JEM, 39* (1924), 757–775; "VI. The oxidation of enzymes in sterile extracts of pneumococcus," *JEM, 40* (1924), 405–422, "VII. Enzyme activity of sterile filtrates of aerobic and anaerobic cultures of pneumococcus," *JEM, 40* (1924), 423–427, "VIII. Nature of the oxidation-reduction systems in sterile pneumococcus extracts," *JEM, 41* (1925), 285–298.

43. Avery and Cullen, "Hydrogen ion concentration of cultures of pneumococci of the different types in carbohydrate media," *JEM, 30* (1919), 359–378, on 359.

> Knowledge of the physiological activities and immunological characters of bacteria serves not merely the purposes of systematic classification, but contributes to a fuller understanding of the problems of infectious disease. The correlation of these apparently independent characters with pathogenicity and with the occurrence and distribution of recognizable types under a wide variety of environmental conditions is essential to the proper interpretation of the phenomena of infection.

The nature of the "essential" contribution to the understanding of disease was not specified either here or in any of the scientific reports or other papers in this series: the translation from the specific medical problem to the particular set of research questions was not spelled out, and in the later papers the linkage to medical problematics nowhere appears. This type of justification can be used for virtually any type of bacteriological investigation of pathogenic organisms, and—other than focusing research on the pneumococcus—the long-term medical interest of Avery's group did not really constrain or direct the choice of problems.

The change in the research strategy implicit in the published papers was acknowledged in the *Report* to the Corporation for 1921 and attributed to the lack of progress in the development of sera against infections with pneumococci of types other than Type I:[44]

> The study of acute respiratory disease has been continued but along somewhat different lines. The treatment of cases of Type I pneumonia with specific immune serum has been continued...This is only an incidental part of the study, however, since it is believed that the efficacy of this serum has now been well demonstrated and its further employment, as well as its manufacture, should be left to others. The efforts to produce serum effective against the other types of pneumonia have not proved successful and it is believed that the successful treatment of these other forms will have to be attained by some other and new method of approach. Consequently during the past year attention has been given to the study of certain fundamental properties of the bacteria concerned in the etiology of pneumonia.

The "logic" of this series of investigations rested on the possibilities of chemical analysis and chemical classification of substances, and the reductionistic strategy of research. Investigation of proteolytic enzymes led to the study of lipolytic and carbohydrate fermenting enzymes, and then of bacteriolytic enzymes and of the hemolytic activity of the extracts used to investigate the enzymes. This resulted in attempts to identify the substance (hydrogen peroxide) responsible for hemolysis and to study the conditions under which it acts. A series

44. *RC*, Oct 1921, 3:IX, 298–99.

of studies on other oxidation/reduction reactions followed. Each step in this series of studies depended on the preceding ones, and extended or built upon earlier results and practical expertise. Instead of going back and forth between the clinic with its problems and the laboratory, the research stayed in the lab. No attempts were made to "link it back" to the clinic. This series of investigations differs from Avery's earlier work in the indeterminate or unarticulated nature of its link to medical concerns and in a much greater degree of continuity in research assured by the systematic exploration of the possibilities for chemical analysis.

3. THE ROAD TO IMMUNOCHEMICAL SYNTHESIS

When the situation at the Institute allowed for the "more fundamental study of bacteria" and an organic chemist, Michael Heidelberger, willing to collaborate with Avery, joined the staff, Avery embarked again on an attempt to identify the chemical structure of the specific soluble substances that he had isolated with Dochez. When this work began anew in 1921 or early 1922,[45] Avery did not explicitly justify his interest in the "chemical basis of immunological specificity" by an appeal to possible direct medical benefits, but the relations between immunological specificity and immunotherapy had been the basis of much earlier work at the Rockefeller. In 1915, for example, Avery had written:[46]

> The biologic classification of the pneumococcus distinguishes four distinct groups. These types are based upon well defined immunologic differences....These distinctive differences in antigenic properties not only offer a reliable method for the more exact determination of the varieties of pneumococcus, but afford *the only rational basis for the study of immunotherapy in pneumococcal infection.*

The novelty of the postwar strategy lay in the emphasis on the *priority of a chemical understanding* of these immunological differences. An additional reductive step has been added to an earlier translation of the problem: in order to understand why only infections with Type I pneumococcus responded to the immune serum, whereas the sera against Types II and III were ineffective, Avery now believed it necessary to determine the chemical differences underlying the

45. Heidelberger recalls that Avery carried a vial of the specific soluble substance around and tried to entice him to the project by arguing that "the whole secret of bacterial specificity is in this vial;" Michael Heidelberger, "A 'pure' organic chemist's downward path," *Annual review of microbiology, 31* (1977), 1–12.

46. Oswald T. Avery, "A further study on the biologic classification of pneumococci," *JEM, 22* (1915), 804–819, on 816 (emphasis mine).

immunological ones. Accordingly, in 1922 and 1923 research focused on the "chemical nature of this substance, with which the type specificity of pneumococcus is so intimately bound."[47]

Avery's placement of his research on the specific soluble substances within the context of immunological specificity and his chemical approach to this problem fitted well within the dominant trends in immunology at the time: the period 1900–1960 has been described as the immunochemical period of immunology. Immunochemical research was supported both by the medical interests in vaccination and serotherapy and by developments in biochemistry.[48] Bacteriologists studied antigenic complexes of pathogenic bacteria for purposes of classification, diagnosis, and serotherapy during the interwar period.[49] Avery was ideally placed to pursue such investigations since the Rockefeller Institute policy promoted collaborations among scientists with different disciplinary backgrounds; even though he worked in a hospital in a bacteriological department, he secured the cooperation of chemists: first Cullen, with whom he worked on the enzymes, then Heidelberger, and finally Goebel.[50]

The work in the laboratory was governed by the technical imperatives of isolating and purifying the part of the substance responsible for the immunological specificity of the different types of the pneumococcus and by attempts to identify its chemical composition. In view of the initial expectation that, because of its immunological activity, the specific substance would be a protein, Avery and Heidelberger labored to prove that the polysaccharides they isolated were not contaminants. They followed up their identification of the specific soluble substance of Type II as a polysaccharide with identical attempts to specify the composition of specific soluble substances of types III and I.[51]

47. *RBSD*, Apr 1922, 3:X, 193. More generally, Avery regarded the study of the specific soluble substance as "an ideal basis for the beginning of a study of the relation between bacterial specificity and chemical composition," *RBSD*, Apr 1923, 4:XI, 146.

48. Arthur M. Silverstein, *A history of immunology* (San Diego, 1989), 124ff; Löwy, "Murphy" (ref. 4). *BHM, 63* (1989), 356–391.

49. For example, the research of J.A. Arkwright at the Lister Institute in London on intestinal bacteria, of P. Bruce White at the British National Institute for Medical Research on vibrios, of F.W. Andrewes at St. Bartholomew's Hospital, London on salmonella, and of Hans Zinsser at Harvard Medical School on B. thyphosus.

50. Simon Flexner, the Director of the Institute, cited Avery's work as a prime example of the advantages of such collaborations in his pamphlet on the evolution and organization of university clinics. Simon Flexner, *The evolution and organization of the university clinic* (Oxford, 1939), 33–35.

51. They reported initial work on the specific soluble substance of Type III in Oct 1923 and in detail in Apr 1924 (*RC*, Oct 1923, 4:XI, 327, and *RBSD*, Apr 1924, 4:XII, 140–142); work on the specific soluble substance of Type I began in Sep 1924 and gave first results by Apr 1925 (*RBSD*, Apr 1925, 4:XIII, 48, 52–53).

In 1923 Avery was attempting to identify chemically other possible immunologically active components of the pneumococcus.[52] Since Avery thought that the specific soluble substances determined the specificity of immunological reactions but were non-antigenic themselves (because the tests had shown that they could not be used alone to produce an effective serum), he worked simultaneously on an isolation of another component of the bacterial cell which, as he soon could claim, was antigenic but not type specific (and thus also ineffective as an inoculum in serum production). This antigenic component was quickly identified as a protein. Avery and Heidelberger probably attempted to develop a complete chemical characterization of the antigenic complex of the pneumococcus on the assumption that such knowledge was necessary for the production of sera effective against types II and III. They did not state this assumption, however, in the earliest papers or reports on the identification of the substance, and did not suggest how the new chemical and immunological knowledge could lead to an improved therapy for pneumonia. In their paper of 1923, they identified the context as the "relation between bacterial specificity and chemical constitution" and insisted on the relevance of the "comparative study of the immunological relations existing between two different cellular constituents of the same organism."[53]

By 1925, however, the reports specify the link between the research program and the possible clinical applications. Here, the new theoretical model proposed by Avery played an important role. His theory of "antigenic dissociation" attempted to integrate the problems encountered in serum therapy with the newer chemical and immunological findings. It provided the framework for making sense both of the clinical difficulties and of the chemo-immunological findings, and specified the medical relevance of chemo-immunological research. It synthesized the laboratory findings and translated the clinical problem into a research program. The theory of antigenic dissociation took into

52. *RBSD*, Apr 1923, 4:XI, 150–151: "These studies have resulted in observations which indicate that immunity to pneumococcus is related to two entirely distinct bacterial substances. One of them is a protein, immunity to which is very specific as regards pneumococcus but is entirely non-specific as regards type. The second substance is non-protein in nature, in its present form of purification possesses the properties of a carbohydrate, and is to a very high degree type specific. This second substance when injected alone is apparently non-antigenic. These facts have suggested entirely new conceptions concerning pneumococcus immunity."

53. Respectively, Michael Heidelberger and Oswald T. Avery, "The soluble specific substance of pneumococcus," *JEM, 38* (1923), 73–79, on 74, and Avery and Heidelberger, "Immunological relationships of cell constituents of pneumococcus," *JEM, 38* (1923), 81–85, on 81.

account the different immunological responses to the polysaccharide specific soluble substances and to the antigenic proteins on the one hand, and the difficulty of producing effective antisera for Type II and III pneumococci on the other, by arguing that the dissociation of the antigenic complex interfered with effective serum production. Effective serum production depended on the morphological integrity of the cell, or at least on the chemical integrity of the antigenic complex of the cell.[54]

By 1927, all research conducted by Avery's group—which by then included Heidelberger, Goebel, Tillett, Julianelle and Dawson—appeared in the annual reports under the heading "Studies on Antigenic Dissociation." The group's coherent (Avery often described it as "rational") research program had as goals a better understanding of the immunological properties of the pneumococcus and, inseparably and explicitly, the production of effective therapeutic sera:[55]

> The bacterial cell as an antigenic unit consists of a combination of nucleoprotein and carbohydrate in which the latter determined the type-specificity of the whole. This compound antigen is dissociable and the ease with which the linkage between the two cellular constituents is disrupted varies with each of the fixed types. When dissociation occurs...the specific (polysaccharide) haptene is split off leaving only the protein fraction which then functions as a secondary antigen....There is also considerable evidence that similar dissociation goes on in the animal body after the introduction of the whole cell....These observations, now supported by experimental evidence, furnish a basis for understanding the difficulties encountered in attempts to produce an efficient antiserum for Type III pneumococcus. Indeed the principle underlying this phenomenon is perhaps applicable to the other types as well....In the preceding discussion of the theory of antigenic dissociation attention has been drawn to the significance of this phenomenon on the production of potent antipneumococcal sera. Since the evidence thus far available clearly indicated that the most efficient antigen is the one least easily dissociable and that the antigenic potency of any given type of pneumococcus is inversely proportional to the rate and degree of dissociation, attempts have been made to increase the type-specific antibodies in immune sera by special methods designed to prevent antigenic dissociation of the type specific antigen.

Working with Julianelle, Avery tried to fix the pneumococcal cell so as to prevent dissociation.[56] The theory of antigenic dissociation guided other attempts to produce effective sera as well. In these

54. *RBSD*, Apr 1925, 4:XIII, 51–59.
55. *RBSD*, Apr 1927, 4:XV, 223–225.
56. *RBSD* (ref. 47), 246–250; *RBSD*, Apr 1928, 5:XVI, 260–263.

attempts, the accumulating chemical knowledge about the structure of pneumococcal polysaccharides and proteins played a more prominent role. Thus Avery and Heidelberger tried to isolate antigens similar to those of the pneumococcus (in the studies on Friedländer bacillus and gum arabic) and, beginning in 1929, Avery and Goebel worked to synthesize artificial antigens by coupling proteins with polysaccharides.

Avery was convinced that the rational approach to the therapy for pneumonia should be based on attempts to imitate natural immune reactions to the pneumococcus; this conviction underlay the translation of the problem of finding a specific serum treatment for pneumonia into the problem of gaining understanding of the chemical structure of the antigen. Knowledge of how antigens induce immune reactions could be practically applied in the clinic only if natural processes could be adequately mimicked by artificial procedures:[57]

> The problems of specific [cure] and prevention of infection lie in the attempt *to interpret and imitate by artificial immunization* certain protective processes of nature which constitute what we call immunity. In order to *imitate* successfully the natural processes involved in spontaneous recovery from disease it is necessary to know the nature of the underlying immunity developed and clearly exhibited in the specific reactions between the infectious agent and the body tissues of the host....With this end in view, those of us on the hospital staff engaged in the clinical investigation of acute respiratory disease are at present seeking to acquire a more intimate knowledge of the immunological and chemical constitution of the pneumococcus—the most frequent and the most deadly microbial incitants of pneumonia in man....[T]he knowledge of type specificity among pneumococcus has furnished a rational basis for the development of an immune serum which in the treatment of pneumonia due to Type I infection has proved of distinct therapeutic value....The problems relating to the possibility of preventive inoculation and the perfecting curative sera for infections due to pneumococcus of Types II and III are in essence the objectives of our present endeavors.

Avery used virtually the same words to explain his approach in a partially retrospective address to the American College of Physicians in 1932. The rationality to which he appealed consisted of a series of translations by which the chemical substances responsible for inducing immunity against the pneumococcus could be identified, and their functions investigated, so that the working of the entire antigenic complex of the pneumococcus could be chemically described and functionally understood. This understanding could be used as a basis for imitating the "protective processes of nature" in developing therapeutic

57. *RC*, Oct 1927, 4:XV, 141–144.

sera. The translation from knowledge of pneumococcal action to treatment rested on the notion that once we know chemically how a biological process takes place, we can reproduce it, and so obtain a therapy for pneumonia.

Avery presented the results of the first stages of this investigative program in a series of papers published between 1923 and 1929.[58] In 1929, he began to publish the results of the second stage of this program, which involved the preparation of artificial antigens. He continued working on this subject with Walther Goebel until 1934. Later Goebel continued his investigations without Avery's participation in the experimental work.[59]

58. In addition to the papers already cited, these were: Heidelberger and Avery, "The soluble specific substance of pneumococcus. Second paper," *JEM, 42* (1924), 301–316; Avery and Heidelberger, "Immunological relationships of cell constituents of pneumococcus. Second paper," *JEM, 42* (1925), 367–376; Avery, Heidelberger, and Goebel, "The soluble specific substance of Friedländer's bacillus. Paper II. Chemical and immunological relationships of pneumococcus type II and of a strain of Friedländer's bacillus," *JEM, 42* (1925), 709–725; Avery and H.J. Morgan, "Immunological reactions of the isolated carbohydrate and protein of pneumococcus," *JEM, 42* (1925), 347–353; Avery and J.M. Neill, "Antigenic properties of solutions of pneumococcus," *JEM, 42* (1925), 355–365; Heidelberger, Goebel, and Avery, "The soluble specific substance of Friedländer's bacillus. Paper I," *JEM, 42* (1925), 701–707, "The soluble specific substance of pneumococcus. Third paper," *JEM, 42* (1925), 727–745; Goebel and Avery, "The soluble specific substance of Friedländer's bacillus. Paper III. On the isolation and properties of the specific carbohydrates from types A and C Friedländer bacillus," *JEM, 46* (1927), 601–607; Goebel and Avery, "A study of pneumococcus autolysis," *JEM, 49* (1929), 267–286; Heidelberger, Avery, and Goebel, "A 'soluble specific substance' derived from gum arabic," *JEM, 49* (1929), 847–857; Avery and W.S. Tillett, "Anaphylaxis with the type-specific carbohydrates of pneumococcus," *JEM, 49* (1929), 251–265; Avery and Goebel, "Chemo-immunological studies on the soluble specific substance of pneumococcus. I. The isolation and properties of the acetyl polysaccharide of pneumococcus type I," *JEM, 58* (1933), 731–755.

59. Between 1929 and 1934 Avery with Goebel, working occasionally with W.S. Tillett and F.H. Babers, published nine papers with a common title: "Chemo-immunological studies on conjugated carbohydrate proteins." Goebel and Avery, "I. The synthesis of p-aminophenol β-glucoside, p-aminophenol β-galactoside and the coupling with serum globulin." *JEM, 50* (1929), 521–531; Avery and Goebel, "II. Immunological specificity of synthetic sugar-protein antigens," *JEM, 50* (1929), 533–549; Tillett, Avery, and Goebel, "III. Active and passive anaphylaxis with synthetic sugar-proteins," *JEM, 50* (1929), 551–567; Goebel and Avery, "IV. The synthesis of the p-aminobenzyl ether of the soluble specific substance of type III pneumococcus and its coupling with protein," *JEM, 54* (1931), 431–436; Avery and Goebel, "V. The immunological specificity of an antigen prepared by combining the capsular polysaccharide of type III pneumococcus with foreign protein," *JEM, 54* (1931), 437–447; Goebel, Babers and Avery, "VI. The synthesis of p-aminophenol α-glucoside and its coupling with protein," *JEM, 55* (1932), 761–767; Avery, Goebel and Barbers, "VII. Immunological specificity of antigens prepared by combining α- and β-glucosides of glucose with proteins," *JEM, 55* (1932), 769–780; Goebel, Babers and Avery, "VIII. The influence of the acetyl group on the specificity of hexoside-protein antigens," *JEM, 60* (1934), 85–94; Goebel, Avery

The question why effective serum could be made against Type I pneumococcus but not against Types II and III remained the underlying medical concern in this work. This continuity of concern masks important developments, however. As immunochemical knowledge accumulated, the translations became more elaborate and complex. We can follow these evolving translations of the medical problem not in the individual research papers of Avery's group, but in the reports to the Board of Scientific Directors and to the Corporation of the Institute, which fully spell out the components of the theory of antigenic dissociation that guided the group's work. Avery often restated these components in his "Red Seal Records," informal accounts of the state of pneumococcus research that he presented to new researchers in the laboratory. In contrast, the research papers from this period are linked either by the *exploitation of the possibilities of chemical analysis* (identification of the polysaccharide of Type II prompted the identification of the carbohydrates of Type III and I, even though an effective anti-serum for Type I pneumococcus existed, and also led to further refinements in the chemical technique), or *by attempts to generalize about the chemical basis of biological specificity* (comparison of the specific soluble substance of Friedländer's bacillus with the specific soluble substance of the pneumococcus, or study of the antigenic properties of gum arabic), or *by the possibilities of comparison of the antigenic properties of the various fractions of the pneumococcus* (carbohydrates and proteins, live organisms, autolyzed organisms, solutions of bacteria). While the overall coherence of the program was provided by medical interest in artificially imitating natural immune processes and by the theory of antigenic dissociation, continuity in daily research and between the successively published research papers was maintained through the technical opportunities of chemical and immunological tests and by attention to theoretical questions about the chemical basis of immunological reactions.

The indirect role of medical concerns and the guiding role of technical possibilities for synthesizing chemical substances appear clearly in the studies on conjugated carbohydrate proteins. Avery and Goebel strove to produce an antigen chemically so similar to that of the pneumococcus that it would induce immunity against specific pneumococcal infections; technical feasibility and biological interest, however, determined their approach to the goal. Avery and Goebel constantly attempted to probe the exact chemical nature of immunological specificity. They attempted to synthesize not only antigens that

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and Barbers, "IX. The specificity of antigens prepared by combining the p-aminophenol glycosides of diasaccharides with protein," *JEM, 60* (1934), 599–617.

would best approximate those of the pneumococcus, but also antigens (conjugated carbohydrate-proteins) that exhibited minimal chemical differences so that their immunological specificity could be compared.[60]

Medical interest in producing an effective serum thus competed with other evidential contexts. These contexts—of biological specificity, or chemical identity, or antigenic structure—made possible meaningful translations of medical problems into questions for investigation. They often structured both the presentation of results and some of the sequences in the research. But they could also be accorded an independent status and serve as a basis for formulating problems not directly tied to the medical concerns. Thus, in their first paper on the conjugated carbohydrate-proteins, Avery and Goebel wrote: "For the purpose of studying the role which simple sugars of different spatial configuration might play in altering the specificity of proteins, it was thought that it might be possible to combine these different sugars with a given protein and to observe specific differences in antigenic properties of the substituted compounds."[61] Although the search for artificial antigens and the study of the chemical basis of immunological specificity were complementary pursuits, occasionally the two contexts suggested different research strategies. It is not obvious, for example, that properties of chemically similar substances were medically relevant, even if they could serve as bases for generalizations about immunological specificity.

4. BACTERIAL ENZYME DECOMPOSING CAPSULAR POLYSACCHARIDE: THE FIRST ANTIBIOTIC OR A RESEARCH TOOL?

Two distinct evidential contexts alternate in Avery's collaboration with René Dubos on the isolation and investigation of the properties

60. For example, Goebel and Avery, "I. The synthesis of p-aminophenol β-glucoside, p-aminophenol β-galactoside and the coupling with serum globulin" (ref. 59), 521–531; Avery, Goebel and Barbers, "VII. Immunological specificity of antigens prepared by combining α- and β-glucosides of glucose with proteins" (ref. 59), 769–780.

61. Goebel and Avery, "I. The synthesis of p-aminophenol β-glucoside, p-aminophenol β-galactoside and the coupling with serum globulin" (ref. 59), on 521; Cf. Avery and Goebel, "II. Immunological specificity of synthetic sugar-protein antigens" (ref. 59), on 534–535: "The experiment was made all the more exacting by the purposeful choice of two monosaccharides which have the same chemical formula and which differ from each other only in specific rotation and molecular configuration....It will be shown further that each variety of antibody is specifically related to the corresponding component of the antigen; that the antiprotein antibodies exhibit the species specificity of the original protein, and that the antibodies reactive with the conjugated sugar proteins are specific for unrelated proteins containing the same carbohydrate group."

of a bacterial enzyme capable of decomposing the capsular polysaccharides of the pneumococcus. This research line originated in an accidental encounter between Dubos, who was then working on soil bacteria that decomposed cellulose, and Avery, who took the opportunity to inform Dubos about an enzyme capable of decomposing capsular polysaccharides of the pneumococcus. As a result of this conversation, Dubos went to the Rockefeller Institute to work in Avery's laboratory. In 1929, he isolated a bacterial enzyme capable of decomposing the capsule of type III pneumococcus both *in vitro* and *in vivo*.[62]

The translation to the medical problem was direct: encapsulated pneumococci are virulent, the non-encapsulated ones are not. An agent that could remove the capsule might render the bacteria nonpathogenic. But at the same time, the enzyme also interested Avery because it could be used to prove "probably beyond doubt" that "the polysaccharide, and not some impurity carried along with it, is responsible for type specificity."[63] Avery had tried to decompose the polysaccharide in 1923 when working with Heidelberger in order to provide more evidence that the specific soluble substance and not a protein was responsible for specificity.[64] Again, enzyme research appeared in two contexts: developing a therapeutic agent against pneumonia, and using an enzyme as an experimental tool in studying immunological specificity and its chemical foundations. Avery also used the enzyme in his research on transformation.[65] Little trace of the instrumental possibilities provided by the enzyme survive the sequence of published research: Dubos and Avery moved from isolating and purifying the enzyme to testing its effectiveness first in mice, then in rabbits and monkeys, while attempts to stabilize and purify the substance continued.[66] The movement from the laboratory to the

62. Dubos (ref. 1), 73–74.

63. René Dubos and Oswald T. Avery, "Decomposition of the capsular polysaccharide of pneumococcus type III by a bacterial enzyme," *JEM, 54* (1931), 51–71, on 69.

64. Avery listed "Attempts to attack the carbohydrates by means of enzymes, molds, and bacteria, and investigation of the fate of the soluble substances under these circumstances" as work for 1923 (*RC*, Oct 1923, 4:XI, 327). See also Maclyn McCarty, *The transforming principle. Discovering that genes are made of DNA* (New York, 1985), 67–69.

65. McCarty (ibid.), 128–129.

66. The joint papers of Dubos and Avery in their order of publication are: Avery and Dubos, "The specific action of a bacterial enzyme on pneumococci of type III," *Science, 72* (1930), 151–152. "The protective action of a specific enzyme against type III pneumococcus infection in mice," *JEM, 54* (1931), 73–89; Dubos and Avery, "Decomposition of the capsular polysaccharide of pneumococcus type III by a bacterial enzyme," *JEM, 54* (1931), 51–71; T. Francis, Jr., E. Terrell, René Dubos, and Oswald T. Avery, "Experimental type III pneumonia in monkeys. II. Treatment with an enzyme which

clinic structured this research; the sequential testing and purification were placed firmly within the therapeutic context.

A victory for the magic bullet?

When in 1939 Herbert Gasser, the new director of the Rockefeller Institute, surveyed the activities and problems of the Institute, he divided the research done at the Hospital into two categories: "contributions which are of immediate practical significance," and "scientific developments noteworthy because of their originality or completeness."[67] The research of Avery's group appeared under one of these headings in the section on pneumonia, and under the other in the section on immunochemistry. Gasser describes four new therapies for pneumonia in very promising terms. Three of these were developed at the Rockefeller Hospital, the fourth in England. First, the rabbit pneumococcus serum, developed by Goodner and Horsfall (later other members of Avery's group participated as well), began to be used in the clinic in 1936. It brought a dramatic reduction in mortality:[68]

> When Osler wrote his textbook of medicine he called pneumonia the "Captain of the men of death." This position pneumonia still has with its 100,000 deaths per year, and its case mortality of 32 per cent. But it should not have it. In the Rockefeller Hospital the mortality of the pneumonia cases treated with the new rabbit anti-pneumococcus serum is only 3.7 per cent. Could the treatment be used even one-third as effectively in the country at large, there would be the truly magnificent saving of life of 65,000 annually.

The second therapy emerged from Avery's and Goebel's attempts to synthesize artificial antigens. In 1938 Goebel synthesized one that produced a notable antiserum:[69]

> [It] possesses the remarkable property of protecting mice against several other types of pneumococcal infections as well...Thus for the first time in the history of infectious diseases, it has been possible with an artificially compounded antigenic substance containing an aldobionic acid to produce a single serum which has proven effective in the treatment of more than one type of experimental pneumococcal infection. For those familiar with the fields of chemical immunology it is apparent that this work may open a new and practical approach to the prevention and cure of pneumococcal infections in man.

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decomposes the specific capsular polysaccharide of pneumococcus type III," *JEM, 59* (1934), 641–668.

67. Herbert Gasser, "Report of the activities and problems of the Rockefeller Institute," Oct 1939, *Scientific reports, 6:28*, Rockefeller University Archive.

68. Gasser (ibid.), 28–29.

69. *RC*, Oct 1938, 6:XXVI, 51.

A clear result of Avery's "rational approach to therapy," Goebel's synthesis was heralded by Gasser as "a remarkable instance of analysis of disease processes in chemical terms."

The third therapeutic method developed at the Rockefeller was Dubos' and Hotchkiss' "discovery, purification, and crystallization of a new chemical substance capable of attacking all gram-positive organisms so far tested." Although the substance called gramicidin proved toxic to dogs, it seemed "a new lead for the chemotherapeutic treatment of infectious diseases in general."[70] Gasser thought the substance had "extraordinary potency."[71]

We come to the fourth therapy. In 1938 Lionel Whitby, from Middlesex Hospital in London, published the results of treating experimental pneumonia in mice with a sulfonamide derivative, sulfapyridine.[72] Sulfapyridine treatment began at the Rockefeller Hospital in late 1938 or early 1939. By April 1939, Avery's group had studied it thoroughly. They confirmed the "beneficial action of the drug in the outcome of pneumococcal pneumonia" but raised several potential problems (such as drug-fastness of the organism) and pointed to possible side-effects. Their first report concludes with the statement: "The primary toxicity of the compound may limit seriously its use unless means are found of reducing the nocuous effects."[73] Gasser echoed the initial cautious acceptance of sulfapyridine at the Rockefeller:[74]

> One of the things that makes research exciting is the rapidity with which events can take place. Hardly had the rabbit serum been perfected when an important chemotherapeutic agent was introduced in England. As one of those rare freaks of empiricism which now and again occur without scientific warning, a drug was discovered of outstanding merit in the treatment of streptococcal infections; and there was prepared a chemical modification of this drug, which proved to be effective against the pneumococcus. At the present time the final position of the drug, sulfapyridine, and the serum in the therapeutic armamentarium is still under consideration.

The caution was short-lived. In October 1940, Avery believed that "there is still use, under certain conditions, for antipneumococcal rabbit serum, particularly when it is employed in combination with other drugs." Nonetheless, he admitted the superiority of sulfapyridine.

70. *RC*, Oct 1940, 6:XXVIII, 20.
71. Gasser (ref. 67), 30.
72. Worboys (ref. 16).
73. *RBSD*, Oct 1939, 6:XXVII, 152–155.
74. Gasser (ref. 67), 30.

"The relative cheapness of the drug and the ease with which practising physicians can administer it locally made it obvious that within a short time this or some closely related drug would for the most part supplant the use of serum in the treatment of pneumonia. As a matter of fact this has already occurred."[75] A year after its first use at the Hospital, sulfapyridine had vanquished other therapeutic agents against pneumonia in all but exceptional and very severe cases in which serum was also used. It was also applied with serum in Type III infections. At the same time, MacLeod studied "sulfapyridine fastness" and the "occurrence and nature of a substance which annuls the bacteriostatic action of sulfonamide compounds."[76]

The serum treatment developed by Avery and his associates fell victim to the groups' scientific success: it required extensive bacteriological typing and control and a time-consuming and expensive preparation. After years of research, the Rockefeller Hospital regarded pneumonia not as one disease, "but thirty two related diseases, each caused by an organism that has the same body as the other organisms, but differs from the other organisms in the chemical composition of a complex sugar-like substance that makes up the capsule."[77] Sera to combat such complexity had little chance in the market against an easily administered drug like sulfapyridine. Just as the Rockefeller's persistent efforts to develop a therapy based on years of immunochemical research seemed to be yielding positive results, sulfapyridine made practical applications irrelevant. Disappointment lurks behind the reports to the Board of Scientific Directors and the Corporation: "When the sulfonamide drugs more or less supplanted the use of immune serum in the treatment of pneumonia, it appeared for a short time that the work on pneumonia at the Rockefeller Hospital might be forgotten or overshadowed by the striking results obtained with the drug." Perhaps Avery hoped Dubos' results with gramicidin would reestablish the reputation of his group as being "in the front line of chemotherapeutic attack against infectious diseases."[78] Ultimately, this reputation was assured not through the contribution to the clinical treatment of pneumonia but by what Gasser referred to in his report as one of the scientific developments "noteworthy because of their originality and completeness:" the long-standing research on transformation to which Avery and MacLeod returned in 1941.

75. *RC*, 1939–1940, Oct 1940, 6:XXVIII, 18.
76. *RBSD*, Apr 1940, 6:XVIII, 131–136.
77. Gasser (ref. 66), 29.
78. *RC* (ref. 74), 20.

5. TRANSFORMATION

It is worth retelling the often-told story of how Avery identified the substance responsible for bacterial transformation to show the relationship between Avery's work on transformation and his long-term research program.[79] Historians have been interested in whether and when Avery became aware of the genetic significance of the work on transformation, in the continuity in research on the problem in Avery's laboratory, and in the reception of Avery's findings prior to the Hershey-Chase experiments. Relations between Avery's medical interests and his research on transformation between 1929 and 1943 have received less attention, although Dubos and Russell have suggested that Avery delayed focusing on the problem of transformation because the phenomenon lacked medical relevance, and that he returned to it only when sulfa drugs rendered his approach to finding a treatment for pneumonia obsolete.[80] But it does not appear that any significant delay occurred or that Avery thought transformation lacked medical relevance.

When Fred Griffith originally discovered, or "produced," the transformation of one type of pneumococci into another by injecting mice with avirulent Type R pneumococci together with heterologous heat-killed Type S bacteria, he was interested in the epidemiology of pneumonia, specifically in the problem of whether avirulent Type R bacteria change into virulent Type S bacteria *in vivo*.[81] Griffith saw his findings as relevant in this epidemiological context and his paper provided an epidemiological interpretation of the phenomenon. He concluded:[82]

> The experiments on enhancement of virulence and transformation of type suggest an explanation of the manner in which pneumococcus residing as an apparently harmless saprophyte in the nasopharynx acquires disease producing powers. So long as it retains certain potentialities, indicated by the possession of traces of S antigen, the most attenuated pneumococcus may develop the full equipment of

79. Dubos (ref. 11); McCarty (ref. 64); H.V. Wyatt (ref. 10); Nicholas Russell, "Oswald Avery and the origin of molecular biology," *BJHS, 21* (1988), 393–400; Portugal and Cohen (ref. 8); Thomas D. Brock, *The emergence of bacterial genetics* (Cold Spring Harbor, 1990); Alphonse R. Dochez, "Oswald Theodore Avery, Oct 21, 1877–Feb 20, 1955," *BMNAS, 32* (1958), 30–49; Löwy (ref. 9).

80. Russell (ibid.), 397; Dubos (ref. 11), 150–51.

81. Fred Griffith, "The significance of pneumococcal types," *Journal of hygiene, 27* (1928), 113–159. Griffith believed that the phenomenon which he had induced artificially might occur naturally, that avirulent R-type pneumococci might undergo transformation into the virulent S-types.

82. Griffith (ibid.), 157.

> virulence....These considerations which relate to an individual case of pneumonia are capable of application to an outbreak of epidemic disease in a community. Thus the consequences which ensue on the decline of an epidemic are not only an increase in the number of insusceptible individuals but also an alteration in the character of the infective organism.

The Rockefeller took an immediate interest in these findings: "experiments were at once undertaken to verify Griffith's results."[83] Martin Dawson repeated Griffith's experiments, attempting to insure that the heat-killed cultures were indeed not viable.[84] He also tried, initially without success, to achieve transformation in an *in vitro* system, and to specify the conditions under which transformation takes place.[85] The experiments were repeated not only with pneumococci but also with Friedländer's bacilli. Since Friedländer bacillus was known to have a capsule chemically and immunologically extremely similar to that of Type III pneumococcus, the Rockefeller also tried cross-species transformation.[86] The speed with which the researchers at the Rockefeller replicated Griffith's experiments is particularly striking since Avery's laboratory seldom tried to replicate work done elsewhere.

The initial report on transformation experiments does not spell out the relevance of Griffith's findings, other than to suggest "the possible significance of these adoptive changes in the course of infection and in the epidemiology of the disease."[87] The interest in Griffith's experiments, however, can be understood better if we remember that his

83. *RBSD*, Apr 1929, 5:XVII, 212.

84. M. H. Dawson, "The transformation of pneumococal types. I. The conversion of R forms of Pneumococcus into S forms of the homologous type." *JEM, 51* (1930), 99–122 and "The transformation of pneumococcal types. II. The interconvertibility of type-specific S pneumococci," ibid., 123–147.

85. Success of *in vitro* transformation was reported in M. Dawson and R.H.P. Sia, "In vitro transformations of pneumococcal types," *JEM, 54* (1931), 681–710. In 1930 Dawson left the Rockefeller Institute for the College of Physicians and Surgeons, where he continued working on transformation.

86. They succeeded in inducing transformation of Friedländer bacilli, though not with Friedländer bacilli injected together with heat-killed Type II pneumococci. The cross species experiment was justified by previous chemo-immunological studies that had shown a close similarity between the specific soluble substances of Type B Friedländer bacilli and Type II pneumococci. These experiments with reversion in Friedländer bacilli seem not to have been pursued. Ref. 83, 227–229.

87. Ref. 83, 205. Dawson's papers place his research in the same context: "The conversion of relatively avirulent pneumococci into highly virulent organisms is obviously a matter of considerable biological and epidemiological significance," Dawson, "I" (ref. 83), 118; and "comparable phenomena may play a role of great importance in many infectious processes," ibid., 121.

findings, on the one hand, seemed counter to the stability of immunologically distinct types of pneumococcus on which Avery had based his entire research program, and, on the other hand, they contributed to the widespread research on S to R variation of bacteria.

After Joseph Arkwright, working at the Lister Institute in London, had described the characteristics of the R/S variation in the enteric bacteria in 1921, many bacteriologists, particularly in the United States, studied it in a large number of bacterial species. The R/S dissociation was linked to antigenic properties of bacteria, as well as to their virulence and morphology. Its apparent relevance for problems of bacterial pathogenicity and immunogenicity, the possibility that it played a role in the rise and fall of epidemics, and its practical bearing on diagnostic procedures, vaccine production, and the classification of bacteria, made it a favorite subject of study during the inter-war period.[88] Dawson had been working on the R/S dissociation of the pneumococcus for several years before the publication of Griffith's paper, while Julianelle had devoted some of his attention to the R/S dissociation of the Friedländer bacillus.

Griffith's findings must also have worried the Rockefeller group insofar as they demonstrated the possibility that the specific types of the pneumococcus, which Avery and his group had proved to be antigenically and chemically distinct, could be transformed into one another.[89] Even if their medical implications were not immediately specifiable, Griffith's experiments were relevant to the main research of the laboratory. Research on transformation continued at the Rockefeller; after Dawson left, first Alloway, then Rogers, and then MacLeod and eventually McCarty as well as Avery himself pursued this line of investigation.

Dawson soon reproduced transformation in a test tube and Alloway turned to the isolation of the bacterial substance responsible for the phenomenon. In 1931, Alloway described his attempts "to extract from type specific pneumococci, the substance or substances responsible for the activation of the R forms" in order to be able to characterize its "chemical and biological properties."[90] Efforts at isolation,

88. Amsterdamska (ref. 3); Joseph A. Arkwright, "Variation," in *A system of bacteriology in relation to medicine*, (London, 1930), *1*, 311–374; Philip Hadley, "Microbic dissociation," *Journal of infectious diseases, 40* (1927), 1–312, and "Further advances in the study of microbic dissociation," ibid., *60* (1937), 129–192; Werner Braun, "Bacterial dissociation. A critical review of a phenomenon of bacterial variation," *Bacteriological reviews, 11* (1947), 75–114.

89. Cf. MacLeod (ref. 5), 5.

90. *RBSD*, Apr 1931, 5:XIX, 336, 337; J.L. Alloway, "The transformation in vitro of R pneumococcus into S forms of different specific types by the use of filtered pneumococcus extracts," *JEM, 55* (1932), 17–31, and "Further observations on the use of pneumococcus extracts in effecting transformation in vitro," *JEM, 57* (1933), 265–278.

purification, and chemical identification of the active substance continued throughout the early 1930s. The early reports say nothing about the interest of the phenomenon beyond affirming its "wide biological significance," but by 1935, after MacLeod began working on the problem, the significance was specified:[91]

> The study is being continued with the hope that knowledge of this important cellular mechanism may lead to a better understanding of the principles involved with specific transformation and induced variations of living cells, not only of Pneumococcus. Furthermore, the thought suggests itself that were we in possession of knowledge pertaining to the nature of the substances which serve as activators and inhibitors of capsule-producing enzymes, the knowledge gained might afford a new approach to a specific attack directed toward the suppression of the capsular function upon the activity of which the pathogenicity of Pneumococcus depends.

Similar assertions about biological importance for the understanding of "variations of living cells, not only of the pneumococcus," and about the possible medical significance of the identification of the transforming agent occur in the reports in 1941, when MacLeod returned to the problem.[92] While the unspecified biological interest in the phenomenon coexisted with a possible medical interest, research was governed by the goal of a chemical characterization of the active substance and the technical means of achieving such chemical identification. The medical interest did not disappear: as late as 1942, Avery, MacLeod, Horsfall, and McCarty devoted their time to the study of virulence of the pneumococcus using transformation as a tool for testing whether "the property of virulence possessed by pneumococci, although only manifest in the presence of intact capsulae, is also dependent upon some other cellular function."[93]

Rockefeller researchers seldom wrote down their speculations about the broader biological or medical significance of the phenomenon. Early on, after testing whether the specific soluble substances themselves could induce transformation (and finding they could not), Alloway speculated that the active substance might

91. *RBSD*, Apr 1935, 6:XXIII, 177.

92. The assertion of medical relevance is repeated almost verbatim from the 1935 report in *RBSD*, Apr 1941, 7:XXIX, 145, and in RC, Oct 1941, 7:XXIX, 23–24. The last contains the sentence: "Such a statement [about the suppression of the capsular function upon the activity of which the disease-producing properties of the pneumococcus depend] might be interpreted as dealing with a new approach to the prevention and cure of pneumonia."

93. *RBSD*, Apr, 1942, 7:XXX, 130; the entire report on research on transformation is devoted to exploring virulence.

function as a co-zymase,[94] but no further hypotheses about the biological nature of the phenomenon occur in any of the reports before 1943. That report, written after the identification of the active agent with desoxyribonucleic acid, reads:[95]

> Thus, the transforming principle—a nucleic acid—and the end product of the synthesis it evokes—the Type III polysaccharide—are each chemically distinct and both are requisite in the type specific differentiation of the cell of which they form a part. *The former has been likened to a gene, the latter to a gene product, the accession of which is mediated through enzymatic synthesis.* The genetic interpretation of this phenomenon is supported by the fact that once transformation is induced, thereafter without further addition of the inciting agent both capsule formation and the gene-like substance are reduplicated in the daughter cells. The changes induced are therefore not transient modifications but are transmitted through innumerable transfers in ordinary culture media.

The final paper, submitted for publication in November of the same year, as well as Avery's famous letter to his brother (May 1943), discuss the possibility that the substance may function as a gene and that it may be a virus.[96]

Avery's approach here paralleled the one he had used in his studies on specific soluble substances and on C-reactive proteins. In each case, Avery first tried to purify and identify the chemical nature of the responsible substance. The importance of these methodological concerns and of the day-to-day instrumental problems emerges from McCarty's account of his collaboration with Avery. In describing their research practice, McCarty emphasized precisely the technical constraints and concerns that guided the experiments that led to the publication in 1944 of the paper on transformation. To cite just one example:[97]

> It was at this point that we applied the treatment with the SIII enzyme, carrying out the reaction until the material no longer gave a detectable

94. Ref. 90, 337.

95. *RBSD*, Apr 1943, 7:XXXI, 151–152 (emphasis mine). This is probably Avery's first written indication of the specific genetic significance of his finding.

96. Avery, MacLeod, and McCarty (ref. 6); Avery to Roy Avery, 26 May 1943, reproduced in Dubos (ref. 11). Löwy ((ref. 10), 112–114) argues that Avery and his collaborators believed that "the transforming principle" activated or modified or determined enzymatic activities, but never suggested that it coded "for the totality of the structure of proteins." While Löwy might well be correct in claiming that the new meaning of "genetic information" emerged only in the 1950s, Avery and his colleagues may not have relied on any definite conception of the mechanism of gene action: Avery explicitly refused to speculate about this matter pending further *chemical* investigations.

97. McCarty (ref. 64), 150–151.

> precipitate with type III antisera. After repetition of the Sevag procedure for removal of the enzyme protein that had been added, the preparation was ready for the final stages of purification....Thus, by careful precipitation of the DNA at the minimal concentration of alcohol required, we should leave behind any remnants of other substances—protein, carbohydrate, or ribonucleic acid—that still remained in the preparation...I don't mean to imply that things always went smoothly as we undertook to prepare several lots of this kind of material. There were a number of hitches along the way, and some modifications in the procedure were necessary....We even had some problems with simple fundamental operations, like growing type III pneumococci for extraction.

Chemistry and instrumental opportunities, as well as the daily problems with experimental techniques and materials, directed the research process, not biology or potential medical applications. Until the substance had been isolated and identified, Avery would refrain from pursuing wider biological or medical significance. He explicitly articulated this strategy in his often-quoted letter to his brother:[98]

> Sounds like a virus—may be a gene. But with mechanisms I am not now concerned—One step at a time—and the first is, what is the chemical nature of the transforming principle? Someone else can work out the rest....today it takes a lot of well documented evidence to convince anyone that the sodium salt of desoxyribose nucleic acid, protein-free, could be endowed with such biologically active and specific properties, and this evidence we are now trying to get.

Avery later defended his reluctance to speculate in public about the nature of the phenomenon he investigated:[99]

> Various interpretations have been advanced as to the nature of this phenomenon. However, those of us actively engaged in the work have for the most part left matters of interpretation to others and have chosen rather to devote our time and thought to experimental analysis of the factors involved in the reaction. This is not to say that we are indifferent and have not among ourselves indulged in speculation and discussion of the relation of the problem to other similar phenomena in related fields of biology.

Both the medical and theoretical biological concerns thus vanished from laboratory experimental practices and did not significantly link one experiment to another. The continuity was provided instead by attempts to gain a more complete chemical understanding of the transformation system and to develop better purification and

98. Avery to Roy Avery (ref. 95), 219.
99. *RBSD*, Apr 1947, 7:XXXV, 126.

identification procedures.

Eventually, of course, the evidence provided by Avery's and his co-workers' identification of the substance responsible for transformation became relevant in the context of molecular genetics. That broke the previous ties to therapy for lobar pneumonia and with the immunological theory central to Avery's earlier biological interests.

6. CONCLUSION: FROM MEDICINE TO BIOLOGY

Before World War I, clinical problems were translated into limited research projects expected to contribute directly to therapy. Research that did not promise direct returns to the clinic was marginalized. Want of continuity in research resulted. The war, which temporarily reduced the institutional autonomy of the Rockefeller Hospital, exacerbated this tendency; research fell under the influence of military medicine.

The postwar return to the research on the pneumococcus initially emphasized "theoretical interest" over "practical relevance." A rhetoric stressing the need for "the study of certain fundamental properties of the bacteria" contained no explicit translation of specific medical problems into particular research projects. The studies of pneumococcal enzymes, nutrition, and the hydrogen-ion concentration exhibited such a pattern. Their occasional medical justifications are phrased in very general terms, play a tangential role in specifying research sequences, and appear largely legitimate. In contrast to the clinically driven studies of the pre-war period, research was governed directly by the available technical opportunities and made relevant within specific biochemical evidential contexts. Consequently, it was pursued more systematically and exhibited more continuity.

By the mid-1920s, Avery had translated the problem of an effective serum treatment for pneumonia into an immunochemical problem of the chemical basis of the biological specificity of the various types of pneumococci. Eventually he could also specify how accumulating knowledge of the antigenic complex of the bacterium might serve in the development of the therapy. This synthesis—explicated most fully in the theory of antigenic dissociation and predicated on the idea that chemical knowledge could serve as the basis for imitating natural immune reactions—guided much of the research in the late 1920s and through the 1930s, providing it both with continuity and medical relevance. Not all of the inter-war research, however, integrated medical goals and the biological or chemical interpretations so fully. In the research on transformation, for example, not all the translations necessary to place the work in either a specific biological (e.g., genetic) or a specific medical context (e.g., that of controlling the synthesis of

specific soluble substances by the pneumococcus) were fully articulated.

When we view his research career as a whole, Avery appears never to have abandoned his medical goals and concerns: he added new research topics because of their potential medical relevance (Dubos' enzyme, C-reactive protein), and moved from one series of investigations to another (such as the transition from the study of the immunological properties of the specific soluble substances to studies of artificial antigens) with medical interests in mind.

When we look more closely at the course of his research, however, we find biological arguments occurring along with the medical ones; transitions from one series of experiments to another are structured not by medical concerns, but by chemical or biological reasoning or by technical opportunities. Moreover, from this middle distance, other non-medical evidential contexts also make their appearance: the chemical basis of immunological specificity, the potential to explore a finding as a research tool for addressing other problems, and so on. These other non-medical contexts not only made possible the very translations on which Avery's approach to the problem of therapy depended, but also incorporated possibilities for distinct paths of investigation unrelated to the initial medical concerns.

These emergent biological contexts never became dominant in Avery's research. He and his co-workers abandoned the path of translations and adaptations of medical problematics only for short periods of time and left some of the biological opportunities unexplored. Dubos suggests that when Goebel showed in 1925 that "type II pneumococcus and the Friedländer bacillus produced polysaccharides with the same immunological specificity...Avery could have extrapolated from this observation to other types of biochemical phenomena. Instead, he limited the discussion of its significance to the field of bacterial immunology."[100] Avery detoured only to return to the medical problem from which he had started. But if one bit of biomedical research flows into another for non-medical technical and theoretical considerations and if these evidential contexts can serve as a basis for initiating research sequences different from those in which medical effectiveness counts most, then it is not surprising that biomedical sciences can drift away from medicine, that fundamental discoveries can be made in applied medical settings, and that Avery could spend his entire career rationally developing a therapeutic method (which was superseded even before it was put to wider use) by making contributions chiefly to biology. The very "rationality" of his approach to

100. Dubos (ref. 1), 110.

therapeutics allowed him to make major biological discoveries.

The medical contexts appear even more remote when the focus changes to that of day-to-day experimental practices and concerns: here technical considerations take on an overwhelming importance, and the chemical standards and rules of the game lead to searches for better enzymes, more stringent purification procedures, and more quantitative and precise methods of determining immunological specificity. By focusing on these day-to-day laboratory activities, we come to appreciate the mundane difficulties of procuring sufficient amounts of substances to be studied, the vagaries of instruments, techniques, and experimental models. These practical and technical constraints assume particular importance within the context of Avery's insistence that a substance be identified chemically before its functions and significance can be investigated. At this level, not only the medical but also the broader biological contexts might disappear. Sometimes the technical opportunities begin to serve not only as means to an independently specified goal, but as an end in themselves. The search for a chemical characterization of the substance responsible for the transformation of pneumococcal types exemplifies the process: intermediate goals became an end-product, while further interpretations (translations into genetic or medical contexts) were put on hold.

The way we put together the views obtained from our three levels of analysis inevitably and systematically affects our interpretations of the relations among the various contexts. When regarded merely as a day-to-day laboratory activity, research seems dominated by technical considerations and local contingencies play a central role, while the wider contexts within which the tinkering makes sense disappear or function only as a neutral and unproblematic background. Only in the resultant research reports do the various biological or medical contexts explicitly appear. But the contexts invoked in individual research papers remain partial: the continuities and the changing logic of specific research lines, and the manner in which medical or biological problematics structure research sequences, can be understood only when series of papers or reports are considered together.

Published papers do not always specify research contexts. Avery's theory of antigenic dissociation was fully articulated not in the research papers he published, but in the institutional reports he wrote; and he reserved the overall logic of his immunochemical approach for the survey description of research in his laboratory delivered on the occasion of his receiving the Johns Phillips Memorial Prize from the American College of Physicians.[101] These more synthetic descriptions

101. Oswald T. Avery, "The role of specific carbohydrates in pneumococcus infection and immunity," *Annals of internal medicine*, 6 (1932), 1–9.

are not merely legitimations after the fact. From accounts by Avery's collaborators we know that he devoted much effort to the articulation of the logic of his work in what came to be known as the "Red Seal Records," which helped to initiate new arrivals to the laboratory into the research endeavor. The "Red Seal Records" have been described as "beautifully planned discourses" that "dealt with the major lines of pneumococcal research."[102] As Dubos remembered them:[103]

> They were virtuoso performances, in which the theme was developed with logic and clarity, starting from the historical background and ending with the rationale of possible scientific approaches....The continuous effort he made to sharpen and polish the language that he used to convey his concepts enabled him to recognize their ambiguities and inadequacies, and thereby facilitated the formulation of working hypotheses sufficiently well defined to be amenable to experimental testing.

Or, in Hotchkiss' account:[104]

> These gems of perfection were continually revised and repolished. The highly organized presentation was a kind of debate with himself, punctuated with rhetorical questions like, "now, why should that be?" or "what does that all mean?" The auditor who was moved to try to respond, however, quickly found himself overwhelmed—and indeed suppressed—by the ongoing flow of well rehearsed logic...These dissertations probably played a great part in concentrating the attention of his younger collaborators on basic problems.

It might be argued that the orderly development portrayed here results from relying on *post facto* accounts of research presented in scientific papers, official reports, and historical narratives. Perhaps so. But the portrayal of laboratory activities as chaotic, highly opportunistic, and contingent processes is just as surely caused by restricting one's attention to the most immediate and narrow contexts of experimental practices which ignore the broader and more continuous features of research. Sociological laboratory studies that tend to downplay the intellectual embeddedness of laboratory practices and to underestimate the role of articulation in scientific research rely on this deliberate omission of wider context. Knowledge claims appear as contingent constructs and purely rhetorical achievements only when artificially abstracted from their history and from the broader contexts of research and accounting in which they are firmly embedded.

102. McCarty (ref. 64), 122.
103. Dubos (ref. 1), 84.
104. R.D. Hotchkiss, "Oswald T. Avery," *Genetics, 51* (1965), 3 (cited in Dubos, ref. 1, 85).

Ilana Löwy has argued that "biomedical research constantly oscillates between the temptation to escape the constraints imposed by medical practice by fleeing into the realm of pure research, and the need to maintain close contact with the clinics in order to benefit from the rewards recompensing the solutions of medical problems."[105] In fact, flight into the realm of pure research was made possible in 20th-century biomedicine by the very strategy adopted to solve medical problems: the translations used to transform them into researchable questions, the laboratory techniques and models used to study them, and the multi-layered nature of research practice.

105. Löwy (ref. 4), 391.