

## IMMUNOLOGY AND LITERATURE IN THE EARLY TWENTIETH CENTURY: *ARROWSMITH AND THE DOCTOR'S DILEMMA*

by

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Scientific research is at the centre of two important literary works published in the early twentieth century: George Bernard Shaw's play *The doctor's dilemma* (1906), and Sinclair Lewis's novel, *Arrowsmith* (1925). Both deal with medical science, and in both the hero is an immunologist (or, in the terminology of the period, a specialist in the science of immunity). But the images of immunology in Shaw's play and in Lewis's book are very different. Moreover, the same real-life scientist, the flamboyant Sir Almroth Wright and the same immunological theory, Wright's opsonin theory, appear in both works, but in diametrically opposed roles. Wright is the barely disguised prototype of Shaw's hero, the scientist Sir Colenso Ridgeon, and Shaw represents the opsonin theory as the most advanced form of scientific knowledge. The name of Wright is seldom mentioned explicitly in *Arrowsmith* but his opsonin theory is the incarnation of the false theories of immunity fought by Max Gottlieb, the exemplary scientist in the novel.

Why was the young science of immunology honoured by placement at the centre of two major literary works? Why was the study of immunity the right occupation for a literary hero in the early twentieth century? And what is the basis of the differences in Shaw's and Lewis's presentations of this discipline, differences made explicit by their opposed evaluations of the same scientist and the same theory? Answering these questions can help us not only to obtain some new insights into these literary works, but also to understand the evolution of immunology in the context of the rapid but by no means unproblematic penetration of scientific ideas into early twentieth-century medicine.

### I

The scientist who plays such a different role in the two literary works, Sir Almroth Wright (1861–1947), was one of the pioneers of prophylactic vaccination in human beings. He was described by his biographers as an impressive figure, both physically and intellectually. Before turning to medical research, Wright studied literature and law and for the rest of his life he kept up a vast array of extra-scientific interests, publishing besides numerous scientific works, articles, pamphlets and books on such topics as philosophy, social criticism, and women's suffrage, which he opposed. In the

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laboratory he was indefatigable, always enthusiastic about his research. He was also a born fighter, bringing his various professional struggles not only before his colleagues, but the lay public as well.<sup>1</sup>

Wright fought for many years to get official recognition for the heat-killed, anti-typhoid vaccine he developed in 1897–98.<sup>2</sup> When in 1902 he became the head of the departments of bacteriology and pathology at St Mary's Hospital in London, he found a new field of battle, the "vaccine therapy" which kept him busy for the rest of his life. While studying the phagocytosis (ingestion) of pathogenic bacteria by white blood cells, Wright noticed that the ingestion and destruction of bacteria by phagocytic cells was facilitated by the presence of specific antibodies in the serum. The destruction of bacteria by white blood cells in the presence of a specific antiserum had been described first by Denys and Leclef, then studied by Marchand and Mennes;<sup>3</sup> but Wright, who applied the staining methods developed by Leishman to the study of bacterial phagocytosis, was the first to quantify this phenomenon, point to its potential therapeutic importance and give it a name—"opsonisation".<sup>4</sup> In his studies, he stressed the importance of both serum antibodies and of phagocytic cells in fighting invading bacteria. He was thus able to reconcile, at least partially, two opposing views concerning the nature of immunity: that of the "cellular school" (mostly French), led by Elie Metchnikoff, who claimed that immune phenomena were mediated by phagocytic cells only; and that of the "humoral school" (mostly German), led by Paul Ehrlich and Emil von Behring, who claimed that only the specific antibodies in the serum were of importance in immune phenomena.<sup>5</sup>

Wright claimed that the discovery of opsonisation not only shed new light on the phenomena of immunization, but also opened a new era in the therapy of infectious

<sup>1</sup> Biographies of Wright were written by Leonard Colebrook, *Almroth Wright*, London, William Heinemann Medical Books, 1954; and by Zachary Cope, *Almroth Wright, the founder of modern vaccine-therapy*, London, Nelson, 1966. Several chapters of Gwyn Macfarlane's biography of Sir Alexander Fleming deal with Wright's personality and describe in detail the atmosphere in his laboratory at St. Mary's Hospital in London: *Alexander Fleming: the man and the myth*, Oxford University Press, 1984. Wright's scientific achievements are described by H. A. Lechevalier and M. Solotorowski in *Three centuries of microbiology*, New York, San Francisco, and Toronto, McGraw Hill, 1965; and a detailed critical analysis of the practical value of his discoveries for medicine has been made by W. D. Foster in his *History of medical bacteriology and immunology*, London, William Heinemann Medical Books, 1979.

<sup>2</sup> Wright claimed that careful analysis of the incidence of typhoid among vaccinated and non-vaccinated soldiers during the Boer War clearly demonstrated the effectiveness of his vaccine. Not everyone was as convinced. Wright's statistical data, based on rather unreliable army records, concerned relatively few cases. The validity of his statistical methods was contested by the statistician Karl Pearson. A. E. Wright, 'On the results which have been obtained by anti-typhoid inoculation', *Lancet*, 1902, ii: 651; K. Pearson, 'Report on certain enteric fever inoculation statistics', *Br. med. J.*, 1904, ii: 1243–6.

<sup>3</sup> J. Denys and J. Leclef, 'Sur le mécanisme de l'immunité chez le lapin vacciné contre le streptocoque pyogène', *La cellule* [Lierre and Louvain], 1895, 11: 177–221; Fr. Mennes, 'Das Antipneumokkoken-Serum und der Mechanismus der Immunität des Kaninchens gegen den Pneumococcus', *Z. f. Hygiene u. Infektionskrankheiten* [Leipzig], 1897, 25: 413–38; L. Marchand, 'Etude sur la phagocytose des streptocoques atténués et virulents', *Archs Méd. exp. et d'Anat. path.*, 1898, 10: 253–94.

<sup>4</sup> W. Leishman, 'Note on the method of qualitatively estimating the phagocytic power of the leucocytes of the blood', *Br. med. J.* 1902, ii: 73; A. E. Wright and S. R. Douglas, 'An experimental investigation of the role of the blood fluids in connection with phagocytosis', *Proc. R. Soc.*, 1903, 72: 357.

<sup>5</sup> K. A. H. Mörner's 'Presentation Speech of the Nobel Prize in Physiology or Medicine, 1908, to Elie Metchnikoff and Paul Ehrlich', in, *Nobel lectures: Physiology or Medicine*, vol. I, Amsterdam, London, and New York, Elsevier, for the Nobel Foundation, 1967, pp. 269–72; A. M. Silverstein, 'Cellular versus

diseases. He attempted to cure many bacterial diseases, particularly chronic and recurrent ones, by using “therapeutic inoculation”, i.e. immunization with small doses of a vaccine prepared with the bacterium that induced the disease. The rationale behind this treatment was that the vaccine would reinforce the body’s natural defences by stimulating the formation of “opsonising antibodies”, and accelerate the elimination of the invading bacteria by phagocytic cells. But, Wright added, the “vaccine therapy” would work only if administered at specific critical moments in the evolution of the individual patient’s immune response. These critical moments could be found by measuring the patients “opsonin index”, i.e. the capacity of the phagocytic cells of a given patient at a given moment to ingest specific pathogenic bacteria. However, according to Wright, measurement of the “opsonic index” was a very delicate and complicated operation that could be completed successfully only by such highly qualified and well-trained pathologists as the members of his own group at St Mary’s Hospital.<sup>6</sup>

Many patients were drawn to Wright’s laboratory, attracted by the possibility of a cure for chronic bacterial diseases. His research unit, aptly rebaptized the “Inoculation Department”, expanded rapidly and became financially self-supporting. Wright’s success was not, however, universally welcomed. Some doctors contested the efficacy of this treatment and the general validity of Wright’s propositions. They nicknamed him “Sir Almost Wright” and “Sir Almost Wrong”. Wright responded with virulent public attacks on the members of the British medical profession, calling them ignorant, incompetent, complacent and guilty of deceiving their patients.<sup>7</sup> He vigorously criticized lazy physicians who did not bother to learn the complexities of infection phenomena but waited for new therapies which “would achieve the marvellous with little labour”.<sup>8</sup>

Nevertheless, the principle of vaccine therapy was adopted by a significant portion of the medical profession. But the physicians soon found that, contrary to Wright’s affirmations, clinical results were often unimpressive and mostly difficult to evaluate; moreover, the elaborate and time-consuming procedures required to measure the opsonin index were of no use whatever.<sup>9</sup> While vaccine therapy, like other low-efficacy

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humoral immunology: determinants and consequences of an epic 19th-century battle’, *Cellular immunology*, 1978, 48: 208–21.

<sup>6</sup> A. E. Wright, *Studies on immunisation and their application to the diagnosis and treatment of bacterial infections*, London, Constable, 1909, pp. 256–68.

<sup>7</sup> A. E. Wright, ‘The world’s greatest problem’, *Liverpool Daily Post*, 30 August, 1905, in Colebrook, op.cit., note 1 above, appendix B, pp. 264–67.

<sup>8</sup> A. E. Wright, ‘A lecture on the principles of vaccine-therapy’, *Lancet*, 1907, ii: 493–9.

<sup>9</sup> As early as 1912, R. W. Allen, a supporter of vaccine therapy, objected to the opsonin index: “The impression will, no doubt, have been received that I regard the opsonic index as a somewhat unpractical and unsatisfactory guide to the administration of vaccines. This is in fact the view I hold”. *Vaccine therapy: its theory and practice*, London, H. K. Lewis, p. 81. Similarly, Hans Zinsser, in the first edition of his *Resistance to infectious diseases* (New York, The MacMillan Company, 1914) raised doubts about the practical value of the opsonin index. In his *Bacteriology: general, pathological and intestinal*, Philadelphia and New York, Lea and Febiger, 1916, Arthur I. Kendall claimed that “opinions differ widely as to the value of vaccines” (p. 174); and that Wright’s discoveries marked an epoch in bacterial therapeutics “in spite of the practical failure of his opsonin index determination as a theoretical guide to immunisation and treatment” (p. 171). W. B. Wherry explained that, “baffled by the difficulties and uncertainties of the opsonic technique and perhaps justly fearing the dreaded ‘negative phase’ the physician still fixes his eye on the chemical and physical manifestations of disease and largely ignores the parasites whose destruction is the *sine qua non* to

anti-bacterial therapies, occasionally continued to be used by physicians before the advent of chemotherapy, measuring the opsonic index was gradually abandoned, even in the "Inoculation Department".<sup>10</sup> Wright himself gradually abandoned some of his concepts, and although in his first publications he stressed the high specificity of the method he proposed—hence the need to prepare a vaccine from the bacterium isolated from the patient rather than use a stock vaccine—later he claimed that vaccine therapy could also provide non-specific protection.<sup>11</sup>

With the notable exception of opsonisation, Wright made no fundamental contributions either to immunology or to medical practice. He was, however, successful in his efforts to make bacteriological knowledge not only acceptable but indispensable to physicians. Wright, in fact, created a new occupational role—that of the medical bacteriologist<sup>12</sup>—a "hybrid" role that combined the tasks (and the privileges) of the bedside clinician with the methods of a fundamental research worker.<sup>13</sup>

Wright's role as the prototype of a literary hero was connected with his discovery of opsonisation and its therapeutic applications. For Shaw, Wright's opsonin theory incarnated the very essence of scientific progress in medicine. By contrast, Lewis's model scientist Max Gottlieb "was having an agreeable time massacring the opsonin theory".<sup>14</sup> It is not clear if Gottlieb was referring to the clinical use of the "opsonin

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recovery." 'Phagocytes and phagocytosis in immunity', in E. O. Jordane and J. S. Falk (editors), *The newer knowledge of bacteriology and immunology*, Chicago University Press, 1928, p. 877.

<sup>10</sup> Alexander Fleming, writing about vaccine therapy in 1934 (A. Fleming and G. F. Petrie, *Recent advances in vaccine and serum therapy*, part II, London: J. H. Churchill, 1934, pp. 243–446), did not mention the opsonic index, and advised the use of 'stock vaccines' instead of specific individual vaccines for the great majority of patients (p. 255).

<sup>11</sup> Observing the effects of prophylactic antipneumococcal immunizations on the vaccinated population, Wright gradually arrived at the conclusion that vaccination against a given disease also conveys some protection against other diseases. A. Wright and others, 'Observations on the pharmaco-therapy of pneumococcus infections', *Lancet*, 1912, ii: 1701. In 1919 Wright confessed that his "prejudice" (the belief that vaccines are specific) prevented him from observing the non-specific ("collateral") effects of immunization earlier than he did: quoted in Fleming and Petrie, op.cit., note 10 above, p. 409. On the later modification of his position concerning the specificity of the vaccine therapy see also his *Studies on immunization, second series*, London: W. Heinemann, 1944, pp. 168–82; and Colebrook, op.cit., note 1 above, pp. 130–1.

<sup>12</sup> The case of Wright has some of the characteristics of "role hybridization" as described by J. Ben-David and R. Collins in 'Social factors in the origins of new sciences', *Am. Soc. Rev.*, 1966, 45: 311. Wright neither founded an entirely new discipline nor transferred knowledge from one field to another with a lower intellectual status. But when he decided to leave the practice of medicine for laboratory research, he did manage to maintain the relatively higher socio-professional status of the consulting medical specialist: Foster, op.cit., note 1 above, pp. 142–3. He did so by transferring the "content" of the previous occupational role, i.e. consultation with patients, to laboratory research through the development of the Inoculation Department and the direct linkage of laboratory research with individual therapy: measuring the opsonin index of each patient, preparing individualized vaccines.

<sup>13</sup> Wright always insisted that to use a bacteriologist as a mere technician was unethical, claiming that he had to be treated, and rewarded, as a consultant colleague. A. E. Wright, "Vaccine therapy: its administration, value and limitations", *Proc. R. Soc. Med.*, 1910, 3: part 1: 1–10. His activities helped to integrate the bacteriology laboratory firmly into the modern hospital, and contributed to the consolidation of the professional status of medical bacteriologists, a new brand of specialists. After a career in medical bacteriology became a respectable option for medical students, a "second generation" of medical bacteriologists was able to make important advances in this area. Today Wright is often remembered, not for his own professional achievements but as the head of the laboratory in which Alexander Fleming, a member of this "second generation", discovered penicillin.

<sup>14</sup> S. Lewis, *Arrowsmith*, New York and Scarborough, Ontario, The New American Library of Classic Literature, 1961, p. 40.

index”—indeed nearly universally abandoned in the 1920s—or, more generally, to the emphasis on the role of specific antibodies in the phagocytosis and the elimination of pathogenic bacteria—a theory that is still considered basically valid. However, Gottlieb’s attitude to immunology, as depicted in Lewis’s book, rather indicates that he was opposed not only to a particular knowledge claim but to a whole style of research, as personified by Wright. The difference between the visions of immunology in *The doctor’s dilemma* and in *Arrowsmith* reflects the existence, in the early twentieth century, of two distinct visions of immunology. Although both Shaw and Lewis chose an immunologist to represent a “genuine” scientist, their divergent literary images reflected different approaches to immunology, and different definitions of what immunology and medical science in general were and should be.

In Shaw’s play, the hero is a physician, the newly knighted Sir Colenso Ridgeon, a character closely modelled on Sir Almroth Wright, Shaw’s personal friend.<sup>15</sup> In the play, Ridgeon is presented as both an able physician and a gifted laboratory worker. He has recently developed a new and highly efficient treatment for tuberculosis based on specific stimulation of the phagocytic cells. But this treatment is available to only a few patients because Ridgeon is the one physician capable of using the new method properly and he has only a limited number of beds in his hospital ward. The “doctor’s dilemma” is that of allocating scarce medical resources. Ridgeon has to decide whether he will save the life of a poor, elderly, thoroughly honest but not very bright physician, or that of a young, highly gifted and extremely immoral painter.<sup>16</sup> Ridgeon’s final decision, to save his colleague rather than the artist, is influenced not only by ethical considerations but also by his personal interest in the latter’s very attractive wife. He decides to leave the young painter in the hands of the fashionable physician Sir Bloomfield Bonington, who promptly kills him with an inadequate utilization of Ridgeon’s discovery.<sup>17</sup>

Shaw made explicit the ideas that inspired his play in his ‘Preface on doctors’ (1911).<sup>18</sup> In this essay he indulged in some violent attacks on physicians’ clumsy or excessive use of certain medical innovations, their quasi-mystical belief in the latest fashionable medical theory, and their tendency to oversimplification. “We are left in

<sup>15</sup> Their friendship was, however, a tumultuous one: they had quite different views not only on medical issues but also on politics, social issues, woman’s suffrage, etc. Colebrook, *op.cit.*, note 1 above, pp. 189–99. Wright was knighted in 1906, the year Shaw’s play was written.

<sup>16</sup> Colebrook states that Shaw got the idea for his play when, during a visit in Wright’s laboratory in 1905, his host affirmed that “the time is coming when we shall have to decide whether this man or that is worth saving”: *ibid.*, p. 194. R. E. Boxill presents a slightly different version of this event: when a new patient wanted to be treated by the opsonic method Wright asked ‘Is he worth it?’ *Shaw and the doctors*, New York and London, Basic Books, 1969, p. 134.

<sup>17</sup> According to Boxill, Shaw represented Ridgeon as an anti-hero, a monomaniac scientist dehumanized by practising vivisection, and believing that his science gave him power over life and death. Boxill, *op.cit.*, note 16 above, pp. 134–43. Shaw’s vision of his hero was undoubtedly partly critical. It is difficult, however, to reconcile Boxill’s interpretation with, for example, Shaw’s letter to Wright, in which he reported that in his new play Wright made no medical mistakes and was universally loathed in consequence, while the King’s physician made nothing but mistakes and was loved by all. Colebrook, *op.cit.*, note 1 above, p. 194.

<sup>18</sup> On Shaw’s views of medicine and science, see also Boxill, *Shaw and the doctors*, *op.cit.*, note 16 above; J. C. Amalric, *George Bernard Shaw: du réformateur victorien au prophète eduardien*, unpublished doctoral thesis, University of Paris VII, 1976, pp. 488–518; I. Brown, *Shaw in his time*, London, T. Nelson & Sons, 1965, pp. 111–29.

the hands of the generations which, having heard of microbes much as St. Thomas Aquinas heard of angels, suddenly concluded that the whole art of healing could be summed up in the formula: Find the microbe and kill it."<sup>19</sup>

The violence of Shaw's attacks on doctors, his open hostility to vaccination (at least in the form it was practised at the time he wrote his essay), his objection to vivisection and his insistence that doctoring was an art and not a science<sup>20</sup> can convey the impression that he opposed the introduction of scientific methods into medicine. This, however, is not the case. Shaw stressed the importance of a serious scientific approach to medicine and ridiculed only the superficial utilization of scientific innovation by greedy, ignorant and incompetent physicians. According to him, a physician often "draws disastrous conclusions from his clinical experience because he has no conception of scientific method, and believes, like a rustic, that the handling of evidence and statistics needs no experts."<sup>21</sup> Shaw saw medical science as much too serious a matter to be left in unqualified hands; and considered the development of clinical laboratories staffed with competent experts to be important. For him, "the alternative lies between the complete scientific process which can be only brought to reasonable cost by being very highly organized as a public service in a public institution, and cheap, nasty, dangerous and scientifically spurious imitations."<sup>22</sup>

## II

When he wrote his play, Shaw was in all probability being directly informed by Sir Almroth Wright about his research work, ideas and scientific philosophy. Lewis, on the other hand, had no direct contacts in the scientific and the medical milieu before he began *Arrowsmith* in 1922. He therefore needed a mediator. This he found in the person of Paul De Kruif, a young physician and research worker with literary ambitions. In 1922 De Kruif, then working at the Rockefeller Institute, published anonymously a series of articles 'Our medical men' in the *Century magazine*, in which he criticized the medical research at the Rockefeller Institute and in particular the lack of controls in the clinical trials conducted there. As a consequence he lost his job and was thereafter free to help Lewis construct his plot, and furnish not only the necessary scientific background but a scientific philosophy as well.<sup>23</sup>

In *Arrowsmith*, Lewis attempted to paint a broad panorama of American medicine and medical science through the life story of a young physician named Martin Arrowsmith. Arrowsmith starts with a rural medical practice in North Dakota, and

<sup>19</sup> G. B. Shaw, "Preface on doctors," in *The doctor's dilemma*, Harmondsworth, Middx., Penguin Books, 1979, p. 28.

<sup>20</sup> *Ibid.*, pp. 15, 26.

<sup>21</sup> *Ibid.*, p. 27. In contrast to Wright, Shaw considered the use of statistics in medicine as important, and he wrote with high regard of Pearson's studies in biological statistics. *Ibid.*, pp. 34, 66.

<sup>22</sup> *Ibid.*

<sup>23</sup> A detailed analysis of the collaboration of Lewis and De Kruif, and a discussion of the latter's scientific philosophy, can be found in C. E. Rosenberg's 'Martin Arrowsmith: the scientist as a hero', in *idem*, *No other gods*, Baltimore and London, Johns Hopkins University Press, 1976, pp. 123-32. See also Mark Schorer, *Sinclair Lewis: an American life*, New York, McGraw-Hill, 1961; P. De Kruif, *The sweeping wind*, New York, Harcourt, Brace & World, 1962, pp. 9-29; Grace Hegger Lewis, *With love from Gracie, Sinclair Lewis 1912-1925*, New York, Harcourt & Brace, 1951, p. 230-58.

then works successively in a public health programme in a small town in Iowa, in the bacteriology laboratory of a fashionable Chicago clinic, and in the “McGurk Research Institute” (representing the Rockefeller Institute) in New York. He finally sets up, with a friend, a research laboratory in the Vermont mountains, far away from the temptations of institutionalized and commercialized science. *Arrowsmith* is a *Bildungsroman* and a moral tale: every stage in Arrowsmith’s life brings him closer to final redemption through pure science. This is described as a conversion to the “religion of science”, and this religion has its prophet, Arrowsmith’s former university teacher and lifelong master, Max Gottlieb.<sup>24</sup> The personality of Max Gottlieb is so central to the novel that at one point Lewis thought of naming the book *In the shadow of Max Gottlieb*. Gottlieb patiently undertakes the education of Arrowsmith. One of his principal messages for his young student is that of respect for the purity of science, and the need to protect it from misuse by “the doctors who want to use therapeutic methods they do not understand” and “want to snatch our science before it is tested and rush around hoping that they heal people”.<sup>25</sup>

Lewis and Shaw both agree that the application of science to medicine is a very serious matter. Both consider it important to distinguish between scientific research of quality and its worthless imitations. Both display the same respect for genuine scientists and a contempt for those who misuse scientific discoveries because they seek fame, money, or both (Sir Bloomfield Bonington in *The doctors dilemma*, Drs Hollabird and Tubbs in *Arrowsmith*). However, the two authors differ in their vision of what genuine scientific research should be, and how it should be utilized. These differences probably stem from the differences between the organization of scientific research in England and the United States, from the divergent social visions of the authors, and, finally, from differences in the scientific philosophy of their informants, Wright and De Kruif. The last was probably the most decisive factor in shaping the final image of science in the two works. Therefore, in order to elucidate the scientific background of *Arrowsmith* and *The doctor’s dilemma*, we have to deal mainly with the authors’ informants.

The science worshipped by Lewis’s heroes is a highly mathematized discipline. In introducing Arrowsmith to his “religion of science”, Gottlieb explains to him that “the only thing necessary is the mathematical analysis of phenomena already observed”.<sup>26</sup> For him the only valid scientific approach is a physicochemical one. He encourages Arrowsmith to study mathematics, because “all living things are physicochemical machines. Then how can you make progress if you do not know physical chemistry, and how can you know physical chemistry without much mathematics?”<sup>27</sup>

It is not difficult to trace the origins of Gottlieb’s scientific philosophy. De Kruif modelled these ideas on those of his scientific hero: the physiologist Jacques Loeb (1859–1924).<sup>28</sup> Loeb, a colleague of De Kruif at the Rockefeller Institute, was one of the

<sup>24</sup> Gottlieb, a German Jew, is ostensibly an atheist, but the young Arrowsmith promptly realizes that in fact he holds religious beliefs of his own: “his just being in a lab is a prayer”. Gottlieb himself declares proudly: “One thing I keep always pure: the religion of a scientist” S. Lewis, op.cit., note 14 above, pp. 31, 267.

<sup>25</sup> Ibid., p. 267–8.

<sup>26</sup> Ibid., p. 266.

<sup>27</sup> Ibid., p. 285.

<sup>28</sup> Information about Loeb’s life and work can be found in his biography by Philip P. Pauly: *Controlling life: Jacques Loeb and the engineering ideal in biology*, New York and Oxford, Oxford University Press, 1987; in

most important figures in early twentieth-century biology. Author of the much discussed *Mechanistic conception of life* (1912), he fought all his life against vitalism in biology. A convinced mechanist, he firmly believed that all the manifestations of life should be studied by physicochemical methods.<sup>29</sup> He thought that a mechanistic approach to experimental biology would form the basis not only of physiology but also of general pathology and therapeutics and, according to Loeb's biographer Pauly, would also allow mankind to direct life at will.<sup>30</sup>

In creating the scientific personality of Max Gottlieb, De Kruif attributed Loeb's scientific philosophy to him in a practically unaltered form, but he did change his profession and his subject of research. Loeb was a physiologist, Gottlieb was an immunologist. This modification needs an explanation since it is not required by the plot: one can imagine Martin Arrowsmith influenced by a physiology teacher and working on protein chemistry. The change can be partially explained by De Kruif's own training as a bacteriologist; he probably preferred to deal with a subject he knew better (although some of his descriptions of Gottlieb's scientific achievements are closer to science fiction than to the actual immunological knowledge of his time). But making Gottlieb an immunologist also helped De Kruif and Lewis to make explicit their opinions about science and its place in society through the theme of the fight against infectious disease, a topic much more interesting for the lay public than Loeb's physiological studies. Moreover, developments in immunology in the 1920s were particularly pertinent to illustrate the scientific philosophy professed by De Kruif.

In his article 'Martin Arrowsmith: the scientist as a hero'<sup>31</sup> Charles Rosenberg explains Gottlieb's scientific position as a part of the struggle between materialists and vitalists in biology. In general terms this is undoubtedly true. Gottlieb's overall philosophy was indeed a faithful reflection of De Kruif's understanding of Loeb's militant monism and materialism. But what about the details? What are the scientific ideas of the bacteriologist and immunologist Max Gottlieb?

When Gottlieb first appears in the book, he is presented as a famous immunologist of German origin, esteemed by a small circle of eminent European scientists. He represents a highly esoteric, mysterious and inaccessible knowledge.<sup>32</sup> Most of his

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the biographical sketch written by his collaborator W. J. V. Osterhout, 'Jacques Loeb', *J. gen. Physiol.* 1928, 8: ix–lix, in G. Corner's *History of the Rockefeller Institute*, New York, Rockefeller Institute Press, 1965, and in D. Fleming's introduction to the 1964 edition of J. Loeb's *The mechanistic conception of life*, Cambridge, MA, Harvard University Press, 1964, pp. vii–xli. In his book, *The Professor, the Institute and DNA*, New York, Rockefeller University Press, 1976, pp. 39–44, René Dubos gives a vivid description of Loeb's impact on his colleagues at the Rockefeller Institute.

<sup>29</sup> Loeb even speculated about the ways "to make the facts of psychology accessible to analysis by means of physical chemistry", op.cit., note 28 above, p.62.

<sup>30</sup> Pauly, op.cit., note 28 above. Loeb claimed that the mechanistic conception of life is the only one which can lead to an understanding of the source of ethics, op.cit., note 28 above, p. 64. Dubos aptly compared this quasi-religious belief of Loeb's with the views expressed by Frederick T. Gates, a Protestant minister and Rockefeller's close collaborator, who founded the Rockefeller Institute and who thought that medical research could be regarded as a new kind of religion: op.cit., note 28 above, p. 41–2.

<sup>31</sup> Rosenberg, op.cit., note 23 above.

<sup>32</sup> His great book *Immunology*, "had been read by seven-ninths of all the men in the world who could possibly understand it—the number of those being nine": Lewis, op.cit., note 14 above, p. 13. R. L. Coard even claimed that, in creating Gottlieb's image, Lewis was inspired by Conan Doyle's descriptions of Sherlock Holmes. 'Sinclair Lewis, Max Gottlieb and Sherlock Holmes', *Mod. Fiction Stud.* 1985, 31: 565–7.



colleagues at the provincial University of Winnemac, where he teaches bacteriology, cannot grasp the importance of his research, of his “long, lonely and failure-burdened effort to synthesize antitoxin”.<sup>33</sup> After twenty years of solitary work and many failures, Gottlieb is successful in producing his masterwork: he synthesizes antitoxin in the test tube. He does so while working for the commercial Dawson Hunziker Company, where he is obliged to take a job after he is driven from Winnemac University. Facing growing pressure to patent and commercialize his discovery prematurely, Gottlieb is saved *in extremis* by an offer from Dr Tubbs, the director of the McGurk Institute, to join his staff and to continue to work there on his great discovery.

When Arrowsmith meets his master at the McGurk Institute, the latter is busy “bringing immunity reactions under the mass action law”, proving that “antigen-antibody combinations occur in stoichiometric proportions when certain variables are held constant”, and “pondering the unknown chemical structure of antibodies”.<sup>34</sup> Gottlieb’s studies at the McGurk Institute belong to the domain of classical immunochemical research. In describing them, De Kruif was in all probability inspired by the works of Loeb’s friend, the Swedish physical chemist Svante Arrhenius (1859–1927). Arrhenius, author of the theory of electrolytic dissociation, later became interested in the physicochemical aspects of the formation of the antigen-antibody bond. He postulated that chemical equilibrium between toxin and anti-toxin follows the ordinary mass action law, a thesis attributed in the novel to Max Gottlieb. Arrhenius was also a scientific model for De Kruif’s friend and collaborator at the Rockefeller Institute, John H. Northrop, the prototype of Terry Wicket in *Arrowsmith*.<sup>35</sup>

Not all Max Gottlieb’s scientific preoccupations, however, can be explained by the evolution of immunology in the early twentieth century. Nothing in the scientific knowledge of his time could justify the success of his “synthesis of antitoxin”. The reader is accordingly kept in complete darkness concerning the procedures Gottlieb used to achieve this revolutionary result.<sup>36</sup> But, even if De Kruif carefully omitted cumbersome technical details, the trend he announced was clear: the future of immunology would lie with the elimination of experimental animals, and the study of chemical reactions in test-tubes. Progress would be made by getting away from the tedious necessity of using a complex, unpredictable and difficult to standardize—in a word, unscientific—experimental model, the living organism. One of Gottlieb’s first discoveries is that “antibodies, excepting antitoxin, have no relation to the immune

<sup>33</sup> Lewis, *op.cit.*, note 14 above, p. 13.

<sup>34</sup> *Ibid.*, pp. 267, 280, 332.

<sup>35</sup> Arrhenius explained his ideas about the theory of immunity in his *Immunochemistry: the application of physical chemistry to the study of biological antibodies*, New York, MacMillan, 1907. This book gave a name to the new scientific specialty dealing with the chemical aspects of immune reactions. For John H. Northrop, Arrhenius was the first to show “that all the various particularities of enzyme reactions could be found in inorganic reactions, and thus began the application of physical chemistry to vital processes.” ‘Biochemists, biologists and William of Occam’, in *The excitement and fascination of science*, Palo Alto, CA, Annual Reviews Inc. 1965, pp. 335–44.

<sup>36</sup> D. Lewis, *op.cit.*, note 14 above, p. 134. Perhaps De Kruif was inspired by Alexis Carrel’s early attempts to induce the production of antibodies by fragments of tissue cultured *in vitro*. A. Carrel and G. Ingebritsen, *J. exp. med.* 1912, 15: 287.

state of an animal”, another step towards the ideal of freeing immunology from living organisms and the drawbacks linked to their study, and directing it toward the realm of pure, unaltered physical chemistry.<sup>37</sup>

Gottlieb deals “calmly and most brutally” with the scientific theories he considers false. Wright’s opsonin theory is cited several times as an example of just such a false theory, and its massacre cheers Gottlieb during the hard times at Winnemac University. The reasons for the choice of this theory to represent a position antithetical to the views held by Gottlieb are not evident at first sight. On the face of it, nothing in Gottlieb’s scientific philosophy should prevent him from acknowledging the existence of specific antibodies that facilitate the ingestion of pathogenic bacteria. And if it were true that Wright’s research was not effected with physicochemical methods, he did stress all his life the importance of quantitative evaluations in medical science, and the need to replace the “empirical method” by a “scientific method” based on pre-existing theoretical constructs.<sup>38</sup> During the long controversy over the effectiveness of vaccine therapy Wright claimed that his method was the only one to permit the correlation of a physiological parameter (opsonic index) with a clinical condition (body temperature) “by the aid of exact quantitative measurements”. He complained that the “ordinary student’s course of bacteriology does not impart any training in accurate quantitative work” and claimed that “serious discipline in quantitative work is an indispensable preliminary to undertaking quantitative bacteriological work for the purpose of diagnosis or guidance in immunization”.<sup>39</sup> Wright’s passionate defence of “science” defined as knowledge expressed in quantitative terms was therefore, at least superficially, similar to the ideas expressed by the fictional Gottlieb and his real-life model Loeb.<sup>40</sup>

The choice of the opsonin theory as the target of Gottlieb’s attacks is, however, easier to understand, considering the goal of Gottlieb’s lifelong endeavour: the separation of research on the production of antibodies from animal physiology and the reduction of all of immunology to physicochemical studies. This vision was perfectly antithetical to the opsonin theory. The very essence of this theory, as Wright formulated it, was firmly to connect the production of antibodies to the physiological state of the whole organism. The therapeutic use of opsonin theory was based on the assumption that, by measuring the activity of the opsonising antibodies in the blood, one could obtain valid information about the general state of the patient’s health and about the progress of his disease. In his book *Studies on immunization*,<sup>41</sup> Wright

<sup>37</sup> Lewis, *op.cit.*, note 14 above, p. 120.

<sup>38</sup> According to Fleming’s biographer Macfarlane, Wright’s “scientific method” was a serious obstacle to the rapid development of the therapeutic use of penicillin. Fleming concluded from his test-tube studies that penicillin could not protect an animal from a fatal infection. A faithful adept of his master and his “scientific method”, he did not make the crucial experiment to verify this assumption, and thus did not realize penicillin’s dramatic therapeutic effects. Fleming, sceptical about its clinical value, was only moderately interested in penicillin between 1929 and 1941: *op.cit.*, note 1 above, pp. 59, 270.

<sup>39</sup> Wright, ‘A lecture’, *op.cit.*, note 8 above.

<sup>40</sup> For example, Gottlieb explained that “up to the present . . . most research has been largely a matter of trial and error, the empirical method, which is the opposite of the scientific method, by which one seeks to establish a general law governing a group of phenomena so that he may predict what will happen”: Lewis, *op.cit.*, note 14 above, p. 59.

<sup>41</sup> Wright, *Studies*, *op.cit.*, note 6 above.

expressed his conviction that the only way to help the organism to get rid of the invading bacteria was to reinforce the natural defences of the body. His own vaccine therapy was a method based on the “physiology of immunization”. Its essential feature was “the scientific exploitation of the protective machinery with which the organism is equipped”.<sup>42</sup> Wright strongly opposed the use of antiseptics (and later of chemotherapy) in bacterial infections, believing that “the antiseptic will not, as the unthoughtful assume, add its antibacterial power to the antibacterial power of the living organism. On the contrary, the antiseptic will directly antagonize the protective forces which the living organism has at its command.”<sup>43</sup>

Thus Wright, who did not define himself as a vitalist, and did not (unlike his friend Shaw) openly support “classical” vitalist ideas, had a strongly anti-reductionist approach to life phenomena. He stressed the holistic aspects of immune phenomena and the importance of the quasi-mystical “protective forces of the organism”.<sup>44</sup>

By situating Max Gottlieb’s scientific controversies in the domain of theories of immunity, De Kruif was able to emphasize one of the implications of the mechanistic conception of life: the need for a reductionist approach to medicine. In so doing, De Kruif echoed his scientific hero, Jacques Loeb. Loeb made many of his admirers among the physicians working in Rockefeller Institute Hospital unhappy by declaring that “medical science” is a contradiction in terms, and that physicians should start by studying the chemistry of proteins if they wanted to be able to find anything useful about disease.<sup>45</sup>

De Kruif never hid his admiration for Loeb and his attitude towards medical science.<sup>46</sup> A physician, trained in bacteriology at the University of Michigan, he started his research at the Rockefeller Institute with a classic bacteriological investigation, the study of bacteria that induce septicaemia in rabbits. He was among the first (together with Arkwright and Zoeller) to describe two variants of the same pathogenic bacterium: the more virulent forming smooth colonies and the less virulent forming granulated colonies.<sup>47</sup> De Kruif showed that the granulated type was a true mutation of the smooth type and that such a mutation existed in nature and could be obtained in the test tube.<sup>48</sup> However, while studying the rabbit septicaemia bacillus De Kruif

<sup>42</sup> *Ibid.*, pp. 256, 324.

<sup>43</sup> *Ibid.*, p. 320.

<sup>44</sup> Some aspects of Wright’s approach to immune phenomena, for example his preoccupation with the balance of body humors, and his belief in the predominance of Nature’s healing forces, do show similarities with traditional nineteenth-century disease concepts. C. E. Rosenberg, ‘The therapeutic revolution: medicine, meaning and social change in nineteenth-century America’, in M. J. Vogel and C. E. Rosenberg (editors), *The therapeutic revolution*, University of Pennsylvania Press, 1979, pp. 3–25. Wright’s mother had worked with Florence Nightingale, who strongly supported the vision of disease as a “reparative process”, and of recovery as a process effected by the body’s normal homeostatic mechanisms. Lechavalier, *op.cit.*, note 1 above, p. 198. C. E. Rosenberg, ‘Florence Nightingale on contagion: the hospital as moral universe’, in C. E. Rosenberg (editor), *Essays for George Rosen*, New York, Science History, 1979, pp. 116–36.

<sup>45</sup> Dubos, *op.cit.*, note 26 above, p. 42.

<sup>46</sup> In 1923 he published a highly flattering portrait of Loeb. P. De Kruif, ‘Jacques Loeb, the mechanist’, *Harper’s Magazine*, January 1923, 146: 182.

<sup>47</sup> P. De Kruif, ‘Dissociation of microbic species: coexistence of individuals of different degrees of virulence in cultures of the bacillus of rabbit septicemia’, *J. exp. Med.*, 1921, 33: 733–88.

<sup>48</sup> *Idem*, ‘Mutation of the bacillus of rabbit septicemia’, *J. exp. Med.*, 1922, 35: 561–74; ‘Virulence and mutation of the bacillus of rabbit septicemia’, *J. exp. Med.*, 1922, 35: 621–9; ‘Rabbit septicemia bacillus types D and G in normal rabbits’, *J. exp. Med.*, 1922, 36: 309–16.

became less and less interested in the pathology of rabbit septicæmia and the growth characteristics of the bacterium, and more and more fascinated by physicochemical studies of the two bacterial variants. In collaboration with Loeb's student and faithful follower J. H. Northrop,<sup>49</sup> he studied the effect of pH alteration on the agglutination of the two types of bacteria, and the relationships between agglutination properties and the isoelectric point of these micro-organisms.<sup>50</sup> The last article published by De Kruif during his stay at the Rockefeller Institute was an attempt to predict the conditions of formation of stable agglutinates of bacteria on the basis of their known physicochemical properties,<sup>51</sup> a quantitative physicochemical study that would undoubtedly have appealed to Max Gottlieb. By presenting reductionism as the only valid approach to the study of infectious disease, De Kruif was therefore also justifying the direction taken by his own scientific research.

### III

At the time *Arrowsmith* was written, the early 1920s, the evolution of immunology made this an appropriate discipline to illustrate a polemic on the validity of reductionism in medical research. In that period, immunology was experiencing a deepening division between a more chemical and reductionistic approach to immune phenomena, on the one hand; and a more medically-oriented and less reductionistic one on the other. This cleavage was a relatively new phenomenon. Although, from its beginnings, the new science of immunology was concerned with both chemical and physiologico-pathological aspects of immunity, at first the two aspects were apparently not contradictory, and indeed seemed to complement each other.

Immunology played a crucial role in winning widespread popularity for the new science of bacteriology. Achievements such as the preparation of efficient vaccines against animal diseases (Pasteur, 1881), the therapeutic effects of the anti-rabies treatment (Pasteur, 1885), and anti-diphtheritic serotherapy (von Behring and Kitasato, 1891), had an important public impact. The general public became interested in bacteria when it became clear that finding the bacterium inducing a given disease led directly to the hope of finding a treatment for this disease through serotherapy, and protection from it through vaccination. As Paul Bert, a nineteenth-century French physician and statesman, put it, "this double discovery—ætiology and virus-vaccines—opened practically unlimited horizons for both pathology and therapeutics."<sup>52</sup> Physicians, at first only moderately interested in Pasteur's work, were "converted" to his theories when they discovered that serotherapy gave them an important therapeutic tool, enabling them, or so they hoped, to cure infectious diseases.<sup>53</sup>

<sup>49</sup> On Northrop's relationship with Loeb see Pauly, *op.cit.*, note 28 above, pp. 169–71.

<sup>50</sup> J. H. Northrop and P. De Kruif, *J. gen. Phys.*, 1921–22, iv: 639–55; P. De Kruif and J. H. Northrop, *J. gen. Phys.*, 1922–23, v: 127–39.

<sup>51</sup> *Idem*, 'Stable suspensions of auto-agglutinable bacteria'. *J. exp. Med.*, 1923, 37: 647–51.

<sup>52</sup> Paul Bert, Intervention during the French Parliament Session no. 2091, 1883.

<sup>53</sup> C. Salomon-Bayet (editor), *Pasteur et la révolution pasteurienne*, Paris, Payot, 1986.

At the end of the nineteenth century and the beginning of the twentieth, immunology also played a key role in the growth of fundamental biological knowledge. Metchnikoff's discovery of phagocytosis (1884) was not only important to the understanding of mechanisms of anti-bacterial immunity, but also the general mechanism of inflammation. It was, therefore, a fundamental contribution to pathology.<sup>54</sup> And, as R. Kohler stressed, the discovery (in the 1890s) of specific antibodies in the serum gave an important stimulus to the development of biochemistry as a discipline distinct from physiological chemistry. The existence of antibodies was considered as proof of the importance of well-defined chemical structures in all important phenomena of life. The principal immunological theory of the early twentieth century, the "side chain theory" developed by P. Ehrlich, was an attempt to link the cell's normal metabolism to the production of antibodies, and to create a uniform "biochemical-immunological" theory of cell functions.<sup>55</sup>

It is true that even during its early years immunology was not free from controversy. Its beginnings were marked by debates on cellular versus humoral aspects of immunity, and even among those who favoured a humoral approach, controversy raged about the exact nature of the antigen-antibody bond. Ehrlich claimed that this was a stable and irreversible chemical bond, the physical chemist Arrhenius argued that antibodies and antigens formed reversible bonds whilst the immunologists Bordet and Landsteiner maintained that antigen-antibody complexes were formed by the physical phenomenon of adsorption.<sup>56</sup> However, notwithstanding these differences of individual approaches, the first generation of immunologists shared the conviction that the physiological, pathological and biochemical aspects of immunity had to be treated as a whole. Both Metchnikoff and Ehrlich viewed immunity as a specific expression of normal physiological mechanisms: for the former it was phagocytosis and destruction of old cells; for the latter, the ingestion of nutritive substances by the cells. And Pasteur's close collaborator Emile Duclaux, the biochemist who succeeded Pasteur at the head of the Pasteur Institute in 1888, stressed the convergence of medicine, physiology, and biochemistry in the studies of microbiology and the identity of preoccupations of immunology and biochemistry.<sup>57</sup> For the first generation of immunologists the clinical aspects of immunology were as important as the fundamental ones,<sup>58</sup> and the science of

<sup>54</sup> Silverstein, *op.cit.*, note 5 above.

<sup>55</sup> R. E. Kohler, 'The enzyme theory and the origin of biochemistry', *Isis*, 1973, 64: 181–96.

<sup>56</sup> P. M. H. Mazumdar, *Karl Landsteiner and the problem of species, 1838–1963*, unpublished Ph.D. dissertation, Johns Hopkins University, 1976; *idem*, 'The antigen antibody reaction and the physics and chemistry of life', *Bull. Hist. Med.*, 1974, 48: 1–21; L. P. Rubin, 'Styles in scientific explanation: Paul Ehrlich and Svante Arrhenius on immunochemistry', *J. Hist. Med.*, 1980, 35: 397–425. In *Arrowsmith Gottlieb*, a physico-chemist, identifies himself with Arrhenius's physicochemical point of view, and emphatically expressed his deep contempt for the organic chemistry which formed the basis of Ehrlich's approach: "Organic chemistry! Puzzle chemistry! Stink chemistry! Drugstore chemistry! Physical chemistry is power, is exactness, is life. But organic chemistry—that is a trade for potwashers". Lewis, *op.cit.*, note 14 above, p. 15.

<sup>57</sup> "Microbiology is connected to the study of one the less known domains of chemistry by the studies of diastases . . . to physiology as a whole by the study of ferments, and to medicine by the study of viruses and venoms." E. Duclaux, *Traité de microbiologie*, vol. I, Paris, Masson, 1898, p. 2. "Immunity . . . becomes more and more the question of diastases and of toxins, which are basically the same thing." *Ibid.*, vol. II, p. 3.

<sup>58</sup> "Immunology, which is already fascinating as a biological science has in addition a great utility for prevention and treatment of disease", F. P. Gay, *Immunology, a medical science developed through animal experimentation*, Chicago, 1910, p. 3.

immunology, in harmoniously combining physiology, pathology, and the chemistry of life “cemented the union between the clinic and the laboratory”.<sup>59</sup>

This unified vision of immunology weakened in the 1920s and signs of this trend could be observed even earlier. The polemic between Ehrlich and Arrhenius on the nature of the antigen-antibody bond reflects not only the differences in research styles of the two protagonists,<sup>60</sup> but also more profound divergences. Ehrlich never lost sight of his main goal: to understand the immunity phenomenon as a part of physiological and pathological reactions of the organism. By contrast, in his studies of antigen-antibody reactions, Arrhenius was interested solely in their physicochemical aspects *in vitro*, not in situating the reaction into the framework of research in cell physiology, even less into the pathology of infectious diseases.

The tendency to separate the study of antigen-antibody reactions from that of infectious disease was accelerated by the discovery, in the 1910s, that specific antibodies could be formed against haptens, artificial chemical structures developed in the laboratory.<sup>61</sup> Before then, immunity was viewed as a defence mechanism of the organism. The physiological vision of immune phenomena, exemplified by Ehrlich’s “side chain” theory, was challenged by the finding that the organism was able to form specific antibodies against man-made structures. Many immunochemists, aware of the shortcomings of the side chain theory, but unable to propose an alternative, gradually abandoned their interest in cells or in the organism as a whole, and consequently their interest in medical problems. Although most continued to refer to the potential impact of their studies on medicine, they concentrated their efforts on detailed physicochemical studies of antigen-antibody reactions in the test tube, and on the fine chemical structure of antigens; as a result they became closely associated with biochemists and protein chemists. Such leading immunochemists as Karl Landsteiner and Michael Heidelberger founded important research schools and under their guidance the immunochemical approach rapidly became fruitful.<sup>62</sup>

The growing importance of immunochemical research programmes was reflected in shifting opinions about the goals of immunological research. In 1920, Jules Bordet affirmed that the science of immunity evolved towards general physiology and biochemistry and that “the defence of organisms against pathogenic micro-organisms, which is now its point of departure, may one day seem far away”.<sup>63</sup> For H. Gideon

<sup>59</sup> “Elle consacre l’alliance de la clinique et du laboratoire”: J. Bordet, *L’immunité dans des maladies infectieuses*, Paris, Alcan, 1920, p. 5.

<sup>60</sup> Rubin, *op.cit.*, note 56 above.

<sup>61</sup> Haptens are small molecules which, when fixed on proteins (“carriers”), elicit the formation of antibodies directed specifically against the hapten. They became a favoured tool of immunochemical research, enabling studies of antibodies directed against simple and well-defined chemical structures: K. Landsteiner and H. Lampl, *Bioch. Z.*, 1918, **86**: 343.

<sup>62</sup> Such important immunochemistry books as *Chemical aspects of immunity*, by H. Gideon Wells (New York: Chemical Catalog, 1925); *The chemistry of antigens and antibodies* by J. R. Marrack (editor), Medical Research Council, Special Report Series no. 194, London, 1934, and *The specificity of serological reactions* by Karl Landsteiner (Springfield, IL, Charles C. Thomas, 1936), summarized the rapid evolutions in this field.

<sup>63</sup> Bordet, *op.cit.*, note 59 above, p. 4. Several years later, M. Lisbonne explained that “finally, as Coca said, the modern science of immunity is dealing with many facts that have only very distant relationship, or none at all, with the immunity against infectious diseases from which it was issued”, ‘L’Immunité et les réactions immunitaires’ in L. Nathan-Larrier (editor), *Traité de microbiologie*, Paris’ G. Doin, 1931, p. 5; and in 1931

Wells, in 1925, immunology was simply a branch of chemistry, one unfortunately still obliged to deal with such hopelessly complex substances as blood compounds and bacterial antigens.<sup>64</sup> J. H. Northrop claimed, in 1928, that immunological reactions were but a specific case of biochemical reactions because “Quantitatively every chemical reaction is specific, and the specificity of immune and enzyme reaction differs only in degree from that of any other reaction. The problem of specificity is one of reactions in general.”<sup>65</sup>

The accomplishments of immunochemists contrasted with the more problematic situation of clinical immunologists. The latter refined the techniques which played a crucial role in diagnosis of infectious diseases (e.g. the Wassermann test for syphilis, the Felix-Weil test for typhus) and greatly improved the classification of bacteria. However, in the 1920s, clinical immunology found itself unable to fulfil its early promise to translate bacteriological progress into therapeutic advance, and thus to contribute to a rapid victory over infectious diseases. Serotherapy, undoubtedly beneficial in many cases, continued to be widely used, and some new vaccines (the most important among them the anti-diphtheria vaccine) were introduced,<sup>66</sup> but the efficacy of many of the vaccines and immune sera was low, and contrary to the early hopes, infectious diseases such as syphilis, cholera, tuberculosis and pneumonia remained major health problems. In addition, the enthusiasm which followed the introduction of serotherapy was moderated by the finding that this technique produced many accidents, some of them fatal. Other therapies based on the application of immunological knowledge to the treatment of infectious disease (vaccine therapy, protein therapy) also continued to be diffused in the 1920s and 30s; physicians were aware, however, of their low clinical efficacy.<sup>67</sup> Research in clinical immunology was then mostly concerned with the diagnosis of infectious diseases and classification of pathogenic germs, and hence continued to be viewed as a “branch of bacteriology”<sup>68</sup>

In the 1920s and 30s the cleavage between the immunochemical and pathological aspects of immunology became more visible. While some immunochemists continued to believe that the progress of knowledge in the chemistry and physics of life would ultimately bring about efficient treatments of infectious diseases, their daily preoccupations rarely concerned pathology. Immunologists dealing with the most advanced techniques of biochemical research sometimes regarded their colleagues the clinically-oriented immunologists with contempt. They considered their methods

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Hans Zinsser summed up his hopes for the chemical future of immunology: “The growing interest in our subject on the part of scholars trained in the fundamental sciences brought us nearer to the understanding of the chemistry of antigens and of the chemical and physical principles of the antigen-antibody reaction . . . This increased application of the methods of fundamental sciences is promising for greater advances in directions of exact knowledge for the coming ten years than are recorded for the ones just passed”. *Resistance to infectious disease*, fourth ed., New York, The MacMillan Company, 1931, p. ix.

<sup>64</sup> Wells, *op.cit.*, note 62 above, p. ix.

<sup>65</sup> J. H. Northrop, ‘The mechanism of agglutination’, in E. O. Jordan and I. S. Falk (editors), *The newer knowledge of bacteriology and immunology*, University of Chicago Press, 1928, p. 801.

<sup>66</sup> W. W. C. Topley and G. S. Wilson, *The principles of bacteriology and immunology*, London: Eduard Arnold, 1936, p. 767; W. Park, ‘The use of human serum from convalescent cases in prevention and treatment’, in Jordan and Falk *op.cit.*, note 65 above, pp. 934–46.

<sup>67</sup> Foster, *op.cit.*, note 1 above, pp. 141–8 L. Thomas, *The youngest science: notes of a medicine watcher*, Oxford University Press, 1984, pp. 26–35.

<sup>68</sup> Topley and Wilson, *op.cit.*, note 66 above, p. 13.

outdated, their experimental systems too complex to permit adequate scientific interpretations, and their results impossible to analyse in quantitative terms. At the same time, clinicians noticed that the progress of immunochemical knowledge still had limited, if any, impact on the solution of concrete clinical problems. Unable to see how the “knowledge that ultimately a human body is a mass of electrons” could bring them “a step nearer to being able to do anything about pneumonia or cardiac disease”, some of them could feel estranged from the reductionist approaches of immunochemists, viewing them as irrelevant to the understanding of pathological phenomena.<sup>69</sup>

#### IV

In making his play's hero an immunologist, Shaw portrayed a representative of a triumphant scientific discipline. Not only was Wright at the height of his own career, he personified the high hopes attached, in 1906, to immunological research and the union between the hospital and the research laboratory. Wright believed that “of all evils which befall man in his civilized state, the evil of disease is incomparably the greatest”, and that “it may be affirmed with confidence of the medical act, as at present practised, that it can do practically nothing to avert death from a virulent bacterial infection or to bring a cure”. But, he added, the reason for medicine's poor showing was not the lack of adequate hygienic conditions but the insufficiency of medical research: “We have not in England any appreciable number of workers engaged upon the task of medical research. This is due to economic reasons.” If their number were greater, and their funding sufficient, spectacular improvement in the therapy of infectious diseases would follow.<sup>70</sup> Wright hoped to convince the rich that, if they cared about their health they should finance medical research, not spend their money on fashionable doctors. Shaw believed that this was not enough. For him, medical research, in order to be efficient, had to become a public service financed by public money. Faithful to his socialist opinions, Shaw also claimed that medical progress alone was not sufficient. He stressed the importance of hygiene, and that what most patients really needed was not medicine but money.<sup>71</sup>

For De Kruif, by contrast, medical research suffered not from lack of money but from the lack of true scientific spirit. He explained that the founder of the Rockefeller Institute, the Reverend Frederick T. Gates, believed that “given enough of the yellow metal, the moolah . . . you can organize all the facilities for grand researchers to discover the cures of all those deaths lamented in the textbook by Dr. Osler”. But, alas, money was not enough: “as the years wore on the hoped-for parade of cures did not come off.”<sup>72</sup> The difference between Wright's and De Kruif's outlooks—and in consequence, between the opinions expressed in *Arrowsmith* and in *The doctor's dilemma*—probably reflected the different statuses of medical research in England and in the United States. Medical research in England, conducted mostly in medical

<sup>69</sup> Dubos, *op.cit.*, note 28 above, p. 42. I discussed this point in my article ‘The epistemology of science of an epistemologist of science: Ludwik Fleck's professional outlook and its relationship to his philosophical works’, in R. S. Cohen and T. Schnelle (editors), *Cognition and fact: materials on Ludwik Fleck*, Dordrecht, Reidel, 1986, pp. 422–5.

<sup>70</sup> A. E. Wright, ‘The world's’, *op.cit.*, note 7 above, p. 202.

<sup>71</sup> Shaw, ‘Preface’, in *op.cit.*, note 19 above, p. 72; Boxill, *op.cit.*, note 17 above, p. 71.

<sup>72</sup> De Kruif, *Sweeping Wind*, *op.cit.*, note 23 above, pp. 20–22.



schools and teaching hospitals, got very limited funding—hence Wright’s need to seek supplementary income through the activities of the Inoculation Department and agreements with the pharmaceutical industry.<sup>73</sup> The situation was quite different in the United States: the 1910s and 20s saw the intensive development of philanthropic foundations which supplied funds for medical research.<sup>74</sup> De Kruif reacted to what he saw as the replacement of devotion to science with devotion to money.

In addition, while Shaw and Wright agreed that medical research, if properly done, would contribute to the well-being of men, Lewis’s hero Max Gottlieb professed a diametrically opposed view. Gottlieb feared that reducing infectious disease, the avowed goal of his own research, would in all probability have disastrous consequences. Freedom from epidemics would, according to him, produce a race so low in natural immunity that “when a great plague, suddenly springing from almost zero to a world-smothering cloud, appeared again, it might wipe out the world entire”. And with the removal of infectious diseases, “the world was grimly certain to become so overcrowded, to become such a universal slave-packed shambles, that all beauty and ease and wisdom would disappear in a famine-driven scamper for existence.”<sup>75</sup> These ideas probably echoed the feelings of Lewis himself. Unlike Shaw, Lewis was not a social reformer. He had a pessimistic vision of an American society which destroyed every able and sensitive individual. He did not advance any concrete propositions about how to change this society, for he did not believe that it was possible to do so. The only solution enabling Martin Arrowsmith to preserve his soul and the purity of his scientific research was to escape into communion with Nature. For Lewis, science was not a way to redeem society, or even to lessen its evils. It could, however, be a way of personal redemption, an individual salvation through the “religion of science”.<sup>76</sup>

*Arrowsmith* was written in a period, the 1920s, when bacteriology and immunology aroused great interest among the lay public—witness the great success of De Kruif’s book *The microbe hunters* (1926), written during his collaboration with Lewis on *Arrowsmith*.<sup>77</sup> However, it had already been suspected that immunology was unable to fulfil its earlier promise of rapid victory over infectious disease. Although in all

<sup>73</sup> Wright’s relationships with the pharmaceutical industry were criticized by his colleagues as a dangerous precedent, which might lead to the limitation of scientific freedom. Colebrook, *op.cit.*, note 1 above, pp. 135–6.

<sup>74</sup> A. Flexner, *Autobiography*, New York, Simon & Schuster, 1960; Corner, *op.cit.*, note 28 above; H. S. Berliner, *A system of scientific medicine: philanthropic foundations in the Flexner era*, New York and London, Tavistock Publications, 1985.

<sup>75</sup> Lewis, *op.cit.*, note 14 above, p. 121.

<sup>76</sup> The ideal of individual salvation through science could also reflect some of Jacques Loeb’s opinions in the 1920s, as reported to Lewis by De Kruif. Loeb’s belief in the general progress of humanity was shattered by the First World War, after which he abandoned his philosophical-political aspirations and saw science as an escape from, rather than a means of dominating the world. Fleming, *op.cit.*, note 28 above, pp. xxxi–xxxiii.

<sup>77</sup> P. De Kruif, *Microbe hunters*, New York, Harcourt & Brace, 1926. In both this book and *Arrowsmith*, De Kruif presented the pioneers of bacteriology and immunology as “bigger than life” heroic figures of the past, living in the mythical “goldene Zeit”: Lewis, *op.cit.*, note 14 above, p. 35. Both works also share a vision of bacteriological and medical research oscillating between the monastic austerity of reductionist laboratory research and the romantic heroism of field work in microbiology. Lewis admired De Kruif’s manuscript of *Microbe Hunters* and convinced his editor Harcourt to publish it. S. Lewis, letters to Harcourt, 7 and 19 July 1923 in Harrison Smith (editor) *From Main Street to Stockholm: Letters of Sinclair Lewis*, New York, Harcourt & Brace, 1952, pp. 135–6.

probability De Kruif continued to believe that bacteriological and immunological research led to important practical results in medicine in the long run, he was probably also aware that such results were neither easy nor rapid. Writing about the medical research of the 1920's, he claimed that "the hoped-for scientific offensive against multiple deaths can hardly be said to have achieved a breakthrough; on wide fronts it can indeed have been said to have fizzled out".<sup>78</sup> Immunology could, therefore, represent for him the relative unfruitfulness of the "old-fashioned" and "non-scientific", i.e. non-reductionist, approach to medical research. For similar reasons, immunology could be, for Lewis, a scientific discipline that could be practised for the sake of pure knowledge, and that could remain free from corruption through success.<sup>79</sup>

Sir Colenso Ridgeon and Max Gottlieb are each a common variant of the myth of the scientist: the missionary and the hermit. Ridgeon represents the scientist-practitioner who brings laboratory knowledge to the attention of the world, and uses his exceptional gifts to help his fellow man. Gottlieb is the genius isolated in his laboratory and indifferent to worldly rewards, who lives solely for the pursuit of pure, esoteric knowledge. Both are immunologists. The differences between the two reflect the differences between the two sides of immunology—a clinically-oriented discipline and a fundamental biological science. At first, the two aspects were intertwined. Immunology's evolution in the early twentieth century and the separation of its scientific aspect from the clinical made it possible for Lewis to describe in 1925 an immunologist who was a pure scientist, unconcerned for the practical and immediate consequences of his research.

The public adopted a new type of a literary hero, the scientist, and the scientists themselves showed interest in their literary representations. This was especially true for *Arrowsmith: The doctor's dilemma* was perceived by the critics rather as a "medical drama". Moreover, although Shaw clearly affirmed in his play, as well as in its printed Preface, his ideas on medicine and on medical research, he was doubtless more concerned with the successful creation of such stage effects as a long death-bed scene than with the presentation of his views on physicians. His critics also preferred the dramatic qualities and shortcomings of the play, rather than its scientific-medical background.<sup>80</sup> Shaw was probably not perturbed by the fact that Sir Almroth Wright walked out indignant during the first performance of *The doctor's dilemma*,<sup>81</sup> nor was he particularly interested in the impact of his play on research workers. By contrast, Lewis, who was very proud of his book's scientific philosophy,<sup>82</sup> insisted on the importance of diffusion of his work among the scientists. In a letter to his editor he recommended that De Kruif should make a list of individual research workers and of

<sup>78</sup> De Kruif, *Sweeping Wind*, op.cit., note 23 above, p. 22.

<sup>79</sup> The last words of the novel are Arrowsmith's joyful declaration: "Probably we'll fail". Lewis, op.cit., note 14 above, p. 430.

<sup>80</sup> Martin Quinn, 'William Archer and The Doctor's Dilemma', *Annual of Bernard Shaw Studies*, 1984, 4: 87–106.

<sup>81</sup> Colebrook, op.cit., note 1 above, p. 195.

<sup>82</sup> Lewis's wife remembered that he was so pleased by his description of Max Gottlieb's summary of what it means to be a true scientist that he considered it worthy of celebration. Grace Hegger Lewis, op.cit., note 23 above, p. 254.

research institutions to which advance copies of *Arrowsmith* should be sent.<sup>83</sup> As one would expect, the reactions of the scientists varied. Thus Sir Macfarlane Burnet, like Arrowsmith one of the pioneers of studies of bacterial viruses, recalled that *Arrowsmith*, when published, created a stir amongst American laboratory workers. He himself greatly enjoyed the story and more or less identified himself with its hero.<sup>84</sup> In contrast, the well-known bacteriologist and epidemiologist Hans Zinsser was greatly irritated by what he perceived as the book's over-sentimental attitude, which he attributed to the misuse of scientific themes by writers such as De Kruif. For Zinsser, if "an epidemiologist on a plague study talked and behaved in the manner of the hero of *Arrowsmith*, he would not only be useless, but he would be regarded as something of a yellow ass and a nuisance by his associates."<sup>85</sup>

When *Arrowsmith* was written, immunology was endowed with enough popular prestige to be an adequate occupation for a heroic literary character. The gradual realization by physicians, and later by the lay public, of the limited practical scope of many immunological innovations probably contributed to the temporary disappearance of the image of immunology as a miracle-making discipline. In contrast to immunochemistry, which after its separation from pathology successfully maintained its high intellectual status in association with biochemical research, clinical immunology lost much of its previous prestige. In the 1930s and 40s it became more and more limited to goal-oriented serological research aimed at the development of diagnostic tools for bacteriology. Moreover, many of its practitioners lacked adequate scientific training. The confusion that prevailed in numerous immunological laboratories made the bacteriologist W. W. C. Topley declare, in the 1930s, that the immunology of his time was "a mixture of established fact, half-knowledge, hopeful guessing and frank bewilderment".<sup>86</sup> Although the scientist remained a familiar figure in the gallery of twentieth-century literary heroes, for many years immunology lost the privilege of providing literary representations of the proper activity of the genuine scientist.

<sup>83</sup> Lewis, letter to Harcourt, 27 December 1924; Smith, *op.cit.*, note 77 above, p. 168.

<sup>84</sup> Sir Macfarlane Burnet, *Changing patterns: an atypical autobiography*, Melbourne, Heinemann, 1968, p. 75. Burnet's enthusiastic reception of *Arrowsmith* can perhaps be related to his deep conviction that "medicine can advance only as a science advances". *Ibid.*, p. 86.

<sup>85</sup> Hans Zinsser, *Rats, lice and history*, London, Macmillan, 1985, p. 13 (first published in 1934).

<sup>86</sup> Quoted by Foster, *op.cit.*, note 1 above, p. 137. P. B. Medawar retrospectively claimed that the immunology of that period "was composed of false empiricism and confused terminology, a mixture of vaccines, antisera and cutaneous tests and nothing else": interview with J. Goodfield in *Cancer under siege*, London, Hutchinson, 1975.