Biotherapies of chronic diseases in the inter-war period: from Witte’s peptone to Penicillium extract

Ilana Löwy

CERMES, Paris, France

Abstract

In the inter-war period physicians elaborated numerous ‘biotherapies’ grounded in the complex interactions between physiology, bacteriology and immunology. The elaboration of these non-specific biological treatments was stimulated by the theory of generalized anaphylaxis that linked the violent reaction to a foreign protein to a broad array of chronic diseases, from asthma and urticaria to rheumatism or chronic colitis. Such diseases were perceived as the result of an ‘abnormal reactivity’ to a sensitisation of tissues and organs by bacteria and by foreign proteins, a view that provided an effective bridge between new concepts derived from bacteriology and immunology and the long-standing pathological tradition. Accordingly, physicians attempted to treat these conditions through specific desensitisation and non-specific biological therapies: peptone treatment, protein therapy, haemotherapy, ‘antivirus’ or ‘opotherapy’. Therapies that attempted to neutralise the harmful effects of chronic infections through ‘desensitisation’ were not seen as marginal medical practices, but were promoted by leading advocates of the ‘Pasteurian sciences’, such as Richet, Widal, Vallery-Radot, Wright and Fleming. They also led to development of new products by the pharmaceutical industry.

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1. Introduction: bacteriology, immunology, anaphylaxis

In Conan Doyle’s story, ‘The adventure of the creeping man’, set in the fall of 1903, Sherlock Holmes is invited to explain the strange, animal-like behaviour of a well known physiologist, Professor Presbury. The riddle is solved when Holmes discovers that the
venerable professor, having fallen in love with a much younger woman, had attempted a rejuvenation cure consisting of a series of injections with an extract of monkey glands. The results were appropriately disastrous. This episode led Holmes to reflect on the dangers associated with the diffusion of such ‘unnatural’ remedies that can only enhance the material and sensual aspects of life, and limit the human striving after spiritual values.\(^1\) The black and white image of science as described by Conan Doyle (himself an M.D.) draws a sharp distinction between the research conducted by honest academic physiologists and the dark, criminal machinations of the suppliers of suspect biotherapies. However, after World War II, a biotherapy, the extract of the mould Penicillium, became the icon of scientific progress. In the Orson Welles movie, *The third man*, dangerous crooks, who operate under the cover of darkness and hide in Vienna’s sewers, adulterate the penicillin supplied to the Austrian capital after the war. The image is again white and black, but it is now the opposite of the one depicted by Conan Doyle, with the dark side of human nature being represented by people who prevent the diffusion of a new, miraculous biological substance. My paper is about the grey transition period, when the precise status of a wide range of biotherapies was not yet fixed, and when the catalogue of Parke, Davis & Company gathered ‘vaccine therapy, serum therapy, phylagen therapy, gland therapy, and diagnostic proteins’ under a single heading: ‘Biological therapy’.\(^2\)

The ‘bacteriological revolution’ in medicine focused the physician’s attention on the specificity of diseases. Vague etiological indications were replaced by a search for specific causes, cures and prophylactics against infectious diseases, an approach summed up in the aphorism (attributed to the French doctor and politician Paul Bert) ‘one disease, one micro organism, one serum, one vaccine’. This point of view was extended to non-infectious pathologies too: cancer researchers looked for ‘germs of cancer’ and investigated ‘resistance to malignancies’, while physiologists became interested in specific nutritive elements and in deficiency diseases. Even Freud’s theories were seen by some as inspired by a search for specific causes and specific cures. The hopes for rapid solutions to the major medical problems were not realized, however. Anti-diphtheria serum, the symbol of specific, laboratory-based therapy for an infectious disease remained a relatively isolated case. Moreover, even this therapy, as the doctors had rapidly learned, was not free of dangers: the repeated injection of animal sera could lead to serious, occasionally fatal anaphylactic shock (that is, a violent reaction to a foreign substance).

Anaphylaxis induced by the injection of a foreign protein was related in the 1910s and 20s to a family of pathologies, including asthma, urticaria or hay fever, all gathered under the broad umbrella term of ‘allergies’. Moreover, during the inter-war period, a broad array of different pathological manifestations from rheumatism and migraine to chronic colitis and ulcers were attributed to ‘systemic anaphylaxis’ and to ‘hypersensitivity’ to foreign proteins. The growing ‘molecularisation’ of biology and medicine in that period should not obscure the parallel existence of perceptions of disease grounded in the pathological tradition. Allergy and anaphylaxis were perceived as expression of an organism’s abnormal reactivity.\(^3\) Accordingly, physicians attempted to treat these conditions through specific ‘desensitisation’ and non-specific ‘biological therapies’ (peptone treatment, protein therapy, haemotherapy), (treatment with blood), opotherapy (treatment with glandular

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2. Parke & Davis (1914, 1926).
The combination of specific and non-specific biotherapies (such as ‘vaccine therapy’) was also used to treat chronic infections. My paper looks closely at a set of ‘biotherapies’ grounded in the complex interactions between physiology, bacteriology and immunology in the inter-war period. It follows the unique configuration which led to the development of holistic theories of disease and non-specific biological treatments in inter-war France, and compares these developments to similar trends in other countries. Here, I will examine the interplay between clinical tinkering, the production of therapeutic substances by small laboratories and the development of new products by the pharmaceutical industry.

2. Anaphylaxis as universal pathogenic principle

Anaphylaxis was first described by Richet and Portier in 1903. Charles Richet (1850–1935) was trained as a physician and physiologist, and combined his scientific activities with numerous cultural and political interests. An enthusiastic supporter of the ‘Pasteurian revolution in medicine’, Richet did not, however, become a true follower of the ‘Pasteurian method’ in the laboratory, and remained faithful to a physiological way of thinking. Richet’s studies of anaphylaxis stemmed from investigations of the physiological effects of toxins. In 1902, Richet and his colleague Portier observed the toxic effect of the extract of marine animals’ tentacles on dogs. Portier and Richet noticed that dogs that survived the first non-lethal injection of the Actinia poison succumbed very rapidly when they received a second dose of the same poison. Portier and Richet coined the term ‘anaphylaxis’ (as opposed to ‘phylaxis’ or prophylaxis = protection) for this phenomenon and noted that the ‘anaphylactic effect’ is produced only if the second injection is given after a sufficiently long lapse of time following the first injection. They also related the diminished resistance against tuberculin exhibited by animals infected with the TB germ to ‘anaphylaxis’.

A year after Portier’s and Richet’s publication, another French researcher, Maurice Arthus, described an anaphylaxis-like phenomenon following repeated injections of horse serum, a non-toxic substance. Arthus immediately linked this observation to the occasionally unfortunate consequences of serotherapy in humans (so-called serum sickness), and to cases of death in humans following the injection of horse serum. Because of the growing importance of serum therapy, ‘hypersensitivity’ to immune and normal serum rapidly became an important subject for fundamental and clinical research. Studies of anaphylaxis in the laboratory focused on links between this phenomenon and immunity. Scientists concluded that the two phenomena were closely related. Anaphylaxis, like immunity, was induced only after an obligatory ‘lag period’ between the ‘sensitising’ and the activating reaction, was highly specific to the sensitising substance, and could be induced by a very

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4 Richet (1933); Wolf (1992); Estingoy (1993).
5 Mayer (1936).
6 Portier & Richet (1902a,b); Richet (1911). See also Estingoy (1993) and (1995–1996), pp. 59–71; (1996). Richet and Portier (the latter rapidly abandoned anaphylaxis studies) were the first to attribute importance to anaphylaxis, but not the first to observe the sudden death of an animal after a second injection of a ‘sensitising’ (often innocuous) substance. Richet (1911), pp. 1–12.
7 Arthus (1903).
8 Von Pirquet & Schick (1905).
small quantity of a foreign protein. The relationship between anaphylaxis and immunity was consolidated through the observation of the passive transmission of the anaphylactic state via the serum of a sensitised animal.

In 1907, Richet attempted for the first time to formulate a hypothesis about the physiological significance of the anaphylactic phenomena. The violence of anaphylactic reactions, Richet argued, may account for their physiological utility. From a teleological point of view—which, he added, should guide every biological investigation—anaphylaxis may be seen as a means for inducing a very rapid reaction to bacterial toxins, and especially to weak doses of these toxins. Anaphylaxis may be seen as an efficient defence reaction, which, nevertheless, can go wrong, especially when sensitising substances are injected into animals (or humans), which is not a natural way to encounter a foreign protein. Three years later, in a talk at the International Congress of Physiology in Vienna, Richet developed a different view of anaphylaxis, focused on its role in shaping the individual pattern of chemical reactions. Each person, Richet explained, had their own unique chemical makeup: ‘each one of us is different from other humans, not only through his mental make up, but also through his chemical constitution’. The body’s humours are able to conserve memories of past events, and the humoral responses are as individualised as neurological reactions. The concept of ‘humoral personality’ was further developed by Richet in his book *Anaphylaxis* of 1911, and in his Nobel Prize speech of 1913. In both, Richet linked experimental anaphylaxis with clinical observations. Medicine, he explained, is familiar with ‘food idiosyncrasy’. Some persons react violently to strawberries, while others cannot eat mussels or crab meat. One should also include in the same category ‘idi-synthetic’ reactions to drugs and different reactions to injection of an immune serum. Richet proposed that all these highly individualized reactions should be seen as forms of anaphylaxis.

In the 1910s, anaphylaxis was seen at the same time as an important biological phenomenon and as a mechanism underlying numerous pathological events. Individual variability is a central problem in medicine, and one may reasonably assume that Richet’s call to study the ‘physiology of the individual’ was related to the medical orientation of his physiological studies. Richet’s aspiration to disengage the studies of anaphylaxis from the

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9 Otto (1906); Rosneau & Anderson (1906).
10 Nicolle (1907).
11 Richet (1907).
13 Richet (1910a).
14 Richet’s innovative concept of ‘humoral personality’ probably has a double origin: studies on anaphylaxis and immunity, and observations on the effects of the central nervous system on internal secretions, another domain that linked chemistry with memory.
15 The phenomenon of ‘sensitisation’ to foodstuffs indicated that some proteins were not entirely digested in the intestine, and could pass intact (or, at least, partially intact) into the circulation. Studies of the passage of proteins from the digestive tract to the bloodstream made between 1905 and 1915 were, however, later abandoned. Only in the 1970s did scientists return to systematic studies of the trans-parietal passage of proteins or their fragments. Richet (1999).
17 I am indebted to Charles Richet’s grandson, Prof. Gabriel Richet, for pointing out to me the centrality of medical goals in his grandfather’s research, and for a discussion of the early links between anaphylaxis and food allergies.
realm of laboratory artefacts and iatrogenic reactions and to link them to human pathologies instead, led him to take a special interest in ‘food idiosyncrasies’. On the other hand, Richet and other physiologists had noted the great uniformity of physiological manifestations of anaphylaxis. Identical anaphylactic phenomena were observed with a wide variety of sensitising substances. This observation, coupled with the connection made between anaphylaxis and numerous chronic diseases led to hopes of finding global physiological cures for these diseases. Paradoxically, the exquisite specificity of anaphylaxis—Richet even mentions the uses of anaphylaxis in forensic medicine in order to identify minute quantities of foreign proteins—was translated in clinical practice into a search for universal, non-specific cures.

The crucial step was the forging of a link between the dramatic manifestations of anaphylactic shock, and more mild and much more frequent pathological phenomena such as allergies. Anaphylaxis was seen as related to immunity, but the failure to demonstrate specific ‘anaphylactic’ antibodies led to the gradual abandoning of this area of investigation by immunologists and serologists. At the same time, physiological investigations of allergic phenomena increasingly focused on efforts to elucidate the mechanisms of non-specific manifestations of allergy and of anaphylaxis, such as the rapid liberation of vaso-dilator and broncho-dilator substances by cells from a sensitised animal. Accordingly, physiologists switched from studies on intact animals to observations of cells and organs suspended in physiological solutions. They demonstrated important analogies between the physiological manifestations of an anaphylactic shock and the effect of beta-iminoazyl-ylamine (histamine) on smooth muscles. In parallel, they displayed the similarities between histopathological changes in the lung of a guinea pig suffering from anaphylactic shock and those present in individuals suffering from bronchial asthma. The latter observation linked experimental studies of anaphylaxis to clinical studies of allergy and serum sickness. Physicians had noted that asthmatic patients often exhibited more severe reaction to the injection of foreign serum and were over-represented among victims of fatal anaphylactic shock. Studies of ‘serum sickness’ and of serum-induced anaphylaxis in humans helped to connect the severe effects of injection of serum or a reaction to an insect sting with the less drastic consequences of sensitivity to foodstuffs, to bacterial substances, and to drugs.

The observation that the injection of foreign serum may lead to a variety of symptoms, ranging from a mild ‘serum sickness’ to a lethal shock, provided an appropriate model for the large spectrum of anaphylactic and allergic reactions in humans. Anaphylaxis and allergy were linked to a broad spectrum of patho-physiological manifestations, especially in chronic diseases. The growing interest in such manifestations can also be related to a greater importance being attributed to functionalist and holistic approaches to medicine in the inter-war era. The great individual variability of allergic and anaphylactic reactions

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18 Richet (1967 [1913]), p. 489.
19 Thus for example Henry Dale proposed in 1916 that every sensitisation with a whole serum was in fact a complex multi-sensitisation. Successive waves of an appearance of a rash in certain patients sensitised by a single injection of serum probably represented the successive appearance, at different intervals, of sensitivity to different serum proteins. The dissociation of specific ‘sensibilins’ in the serum was, Dale concluded, a nearly impossible task. Roodhouse Gloyne (1919).
20 Schultz (1909); Dale & Laidlaw (1911). On the history of histamine see Beaven (1976); Tansey (2003).
21 Kolmer (1917).
(idiosyncrasy) was seen as an example of the variability of the ‘terrain’, and was paradoxically employed as an argument against the development of specific remedies. Effective therapy, some physicians argued, would not be etiologic, but ‘function regulating’, that is, it should above all treat the disease-producing irritability of the organism or its organs. During the inter-war era, this view was energetically promoted in France by Fernand Widal and his collaborators.22

3. ‘Diatheses’ and ‘colloidoclassic shock’: Widal’s physiological treatments

Fernand Widal (1862–1929) was one of the pioneers of medical bacteriology in France. He is known for his studies of typhoid fever (he was the first to develop a blood test for this disease, ‘Widal’s reaction’), and of puerperal fever.23 From 1914 on, Widal became interested in allergic phenomena and argued that they reflect predisposition to an instability of colloids, or, in his terms, ‘colloidal diathesis’ (the term ‘colloids’ described constitutive blocks of living matter, and was replaced later by ‘macromolecules’: diathesis is a nineteenth-century medical term that described a global predisposition to morbidity—it can be related to terms such as ‘terrain’, ‘idiosyncrasy’ or ‘temperament’). Widal’s interest in anaphylaxis and in diathesis was stimulated by his studies of kidney disease, which led him to a holistic and function-centred understanding of pathologies. It also led him to an interest in the physico-chemical composition of body fluids, and of cytoplasm. In parallel Widal, like Richet, strongly adhered to a chemical vision of life, and to a belief that major medical problems would be solved through a better understanding of the physico-chemical properties of cell components: ‘c’est dans le domaine des actes élémentaires de la vie, le monde de la chimie moléculaire et de la chimie physique que la médecine trouvera l’explication dernière des phénomènes pathologiques. Tous en nous se réduit aux réactions des molécules ou des agrégats’.24 In 1913, Widal and his collaborators studied a sheep trader who became allergic to sheep wool and developed severe crises of asthma when near sheep. During these crises, Widal observed changes in the blood, similar to those present during a typical episode of anaphylactic shock. He concluded that allergies, asthma and Quincke’s oedema were ‘anaphylactic diseases’, and that the underlying mechanism was the perturbation of colloidal equilibrium, an event he termed ‘colloidoclassic shock’. Some individuals, he argued, are affected by ‘colloidal diathesis’ (either hereditary or acquired), which makes them susceptible to anaphylactic problems.

Widal attempted to describe as accurately as possible the physiological symptoms of such a shock, noting a decrease in arterial pressure, the diminution of the number of circulating white blood cells and modifications in mechanisms of coagulation of blood. He termed this whole collection of these symptoms a ‘hemoclassic crisis’.25 Widal noted that Pasteur Vallery-Radot had described a similar set of symptoms during experimentally induced anaphylactic shock in rabbits, an observation that strengthened the links between anaphylaxis, asthma and skin allergies.26 Widal proposed that the manifestation of ‘hemo-

22 On the holistic medicine of the inter-war period see Lawrence & Weisz (1998), and especially Weisz (1998), pp. 68–93.
23 Besançon (1929); Lemière (1955).
24 Widal (1932a [1911]), pp. 727–739.
26 Widal, Lermoyez, Abrami, Brissaut, & Joltman (1914).
classic crisis’ induced by anaphylactic phenomena was just a specific case of ‘proteinic shock’ or ‘peptonic shock’ that could follow the injection of whole or partly digested proteins.27 He was joined by his colleagues in arguing that physicians should above all be concerned by these physiological manifestations of ‘hemato-vascular crisis’. Such a crisis could be induced by the injection of foreign protein, by the massive passage of the products of tissue disintegration into the circulation (trauma, surgery, large-scale damage to tissues induced by microorganisms) and by pathological processes that provoked the spontaneous disintegration of cells, such as cold paroxysmal hemoglobinuria (a blood disease described by Donath and Lansteiner). In all these pathologies, the passage of proteins into the circulation induced perturbations of the equilibrium of the body’s fluids. Individuals vary, however, in their predisposition to develop the symptoms of ‘hemoclassic’ or ‘colloidoclassic’ shock, with some being more susceptible than others to the perturbing effects of the presence of these proteins in the circulatory system.28

The next step was to propose therapies based on the notion of ‘colloidoclassic shock’. Such therapies, Widal and his colleagues proposed, should be based on the principle of desensitisation. They could involve treatment by the injections of proteins, bacterial antigens or autologous or heterologous serum. Widal favoured the injections of peptones (products of a partial enzymatic digestions of proteins), and especially of ‘Witte’s peptone’, a semi-standardized preparation that could be purchased commercially. They reported good clinical results with this peptone for the treatment of numerous allergic states. They also noted that in some cases a deliberate induction of ‘colloidoclassic shock’ can have therapeutic virtues, but warned against the unpredictability of the individual patient’s reactions.29 Widal and his collaborators also argued that ‘opotherapy’—treatment using glandular extracts, in particular of the adrenal and thyroid glands—could occasionally induce cures. In 1922, the effects of treatment with non-purified gland extracts could have been attributed both to specific chemical substances in the gland, and to the non-specific effects of the injection of foreign proteins. Widal vacillated between explanations that focused exclusively on the specific activity of gland extracts, and those that also took the non-specific effects of ‘opotherapy’ into consideration.30

In the 1910s and 1920s Widal’s views were widely discussed among French doctors. They inspired the development of a number of non-specific, or semi-specific therapies for chronic pathologies. The chemist Auguste Lumière further developed Widal’s proposal that anaphylaxis is grounded in a modification of physico-chemical properties of cells. Lumière, best known today for his contributions to the beginnings of cinema, was the author of several books in which he explained all the reactions of living matter through the flocculation of colloids. Lumière argued that disturbances of this flocculation of colloids were at the origin of numerous chronic diseases of anaphylactic origin, such as urticaria, dermatosis, arthritis, rheumatism, migraines and asthma. These diseases should therefore be treated by the administration of simple chemical substances, which would stabilise the colloidal equilibrium of the cell and limit chaotic flocculation.31 By contrast,

27 Widal, Abrami, & Brissaut (1920).
28 Researchers had found that a single injection of peptones partly mimics anaphylactic shock. Nolf (1910); Danysz (1920), pp. 114–120.
29 Widal, Abrami, & Brissaut (1921); Widal, Abrami, & Lermoyez (1922).
30 Widal, Abram, & De Gennes (1922).
31 Lumière (1922, 1924, 1932, 1933).
other researchers took Widal’s views as a starting point for the elaboration of biological therapies. The physician and pioneer in blood transfusion, Arnold Tzank, advocated ‘immuno-transfusion’. This treatment could either be specific—the transfusion of blood from an individual who had recently recovered from a given infectious disease to someone suffering from the same disease—or non-specific—the transfusion of normal, heterologous blood. In the latter case, a transfusion constituted a ‘biolactic therapy’ that, like hemotherapy, proteinotherapy, serotherapy or vaccinotherapy, stimulated the body’s own defences.32 Jean Danysz, a bacteriologist at the Pasteur Institute postulated that ‘chronic anaphylaxis’, at the origin of many chronic diseases and ‘idiosyncrasies’, was often induced through contact with proteins from the bacteria in the intestine. He developed and then marketed (on a very modest scale) a preparation made from the extracts of six of the main intestinal bacilli. Repeated injection of this preparation (‘a non-specific but selective bacteriotherapy’) Danysz claimed, led to a significant improvement in gastrointestinal troubles, skin diseases, rheumatism and arthritis, and neurasthenia.33

To sum up, between 1914 and 1930, French clinicians developed a series of holistic theories of disease, grounded simultaneously in the extension of notions of immunity and anaphylaxis to a wide range of pathological phenomena, and in a physico-chemical (or ‘colloidal’) vision of life.34 Such a ‘colloidal vision of life’ (later replaced by a ‘macromolecular’ one), strived to find a single explanation for complex pathological phenomena, and was associated with an attempt to elaborate a unified therapy for all these phenomena. The result was the development of an impressive number of non-specific or semi-specific therapies, usually based on the principal of injecting foreign (and occasionally also autologous) proteins.35 Nearly all these therapies were grounded in clinical practice, and, with the important exception of Besredka’s ‘antivirus’, did not lead to the development of truly marketable products.

4. Besredka on ‘local immunity’ and ‘antivirus’

Alexandre Besredka (1870–1940) was a close collaborator of Elie Metchnikoff at the Pasteur Institute, who would later become the head of the laboratory (‘chef de service’) that Metchnikoff founded. Besredka, like Metchnikoff, was interested in the cellular and physiological manifestations of immunity, and from 1906 until 1913 he focused his research on anaphylaxis.36 His studies on ‘anti-anaphylaxis’ (the attenuation of anaphylactic reaction by intradermal injection of a small amount of the sensitising substance) led him to the development of a unified theory of ‘sensitivity’. Besredka proposed that all the immune phenomena—allergy and anaphylaxis, natural and acquired immunity—were simply different expressions of a single physiological mechanism. The specificity of anaphylactic or immune reactions was not based on the chemical specificity of antibodies in the blood, but, like the ‘specificity’ of natural immunity, reflected the receptivity of target cells to pathogenic germs or, alternatively, their capacity to react to toxins.37 The main
difference between natural and induced immunity, and between the absence of anaphylactic sensitivity and artificially induced desensitisation (treatment by small doses of sensitising substance), was the way in which the end result—the absence of reactive cells—was obtained. A naturally immune or non-sensitised animal is devoid of ‘reactive cells’, while in an artificially immunised or a desensitised animal these cells are either depleted or inactivated. Besredka’s conviction that immunity was grounded in the desensitisation of cells led him to the development of an ‘antivirus’ therapy—the use of filtered supernatants of bacterial cultures for vaccination as well as for the treatment of chronic infections, the main topic for his studies in the 1920s and 30s.

Besredka’s concept of local and cell-based resistance to germs led him to try to develop vaccination through intradermal contact (cuti-vaccination). Besredka claimed that he successfully vaccinated guinea pigs with bacterial cultures, and with extracts of such cultures. He then affirmed that supernatants of old cultures (10–15 days), are especially rich in vaccinating substances. He named these supernatants ‘antivirus’, and later developed therapies against chronic infections using dressings soaked with such an ‘antivirus’. While the theoretical underpinnings of the ‘antivirus’ were quite different from those supporting Wright’s ‘vaccine therapy’ (the antivirus was expected to desensitise cells receptive to a given bacterium; vaccine therapy aimed at stimulating the production of humoral antibodies), in practice their uses were quite similar—therapy of a great variety of chronic infections and other pathologies in which one suspected the involvement of a bacterium. In pre-antibiotic times, chronic infections, even relatively minor ones, were an important medical problem, and physicians welcomed preparations credited with the capacity to control this problem. Thus, surgeons proposed applying Besredka’s preparations to prevent contamination and speed up healing. Following a well established Pasteurian tradition, Besredka established links with laboratories that then produced his ‘antivirus’. He did not receive any direct profits from these links, but used the commercial success of the ‘antivirus’ preparations and physicians’ reports on their clinical efficacy as his main argument against the numerous opponents of his ‘local immunity’ approach.

In the late 1930s, Besredka attempted to interest the directors of the Pasteur Institute in the ‘antivirus’. The main commercial products of the Pasteur Institute at the time were specific antisera. The strong opposition of the Institute’s directors, and especially of Gaston Ramon, the head of the sera and vaccines production unit at Garches, to the production of the antivirus by Besredka’s laboratory, was later described in terms of a scientific controversy. Besredka’s theory of ‘local immunity’, and his insistence on the central role of

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38 To put it in a nutshell, according to Besredka, in immunisation—if one agrees that the immunising substance is an antibody—protection is an inactivation of a ‘reactive’ cell by an antibody; in anti-anaphylaxis—if one accepts the view that ‘sensibilin’ is an antibody—desensitisation is an inactivation of an antibody which makes the cells ‘reactive’. The latter phenomenon can thus be viewed as a return to a normal situation.

39 Besredka (1928). On Besredka’s ‘antivirus’ see Löwy (1998). The ‘antivirus’ can be inscribed in a long tradition of the use of bacterial products to induce a non-specific stimulation of the body’s defenses; among the latter, ‘Coley toxins’, and ‘phylagens’. The Parke & Davis catalogue of 1914 has a large section dedicated to ‘phylagens’—sterilised aqueous solutions of substances secreted by bacteria in culture. Phylagens, prepared according to a method described in 1910 by a Californian physician, Dr. Schaffer, were credited with the capacity to fight ‘mixed infections’. Löwy (1993); Parke & Davis (1914), pp. 103–120.

40 Besredka (1925).

41 Besredka (1930).

42 Dancer (1931), pp. 6–9.
cells and not humoral antibodies in resistance to infection went against the main dogma of the ‘Pasteurians’. One may argue, however, that the controversy was also, and perhaps mainly, over different approaches to the industrial production of biologicals. The Pasteur Institute, an independent foundation (although supported through state and municipal subsidies), was funded through the marketing of vaccines and sera. The institute’s commercial strategy was grounded in maintaining the image of the ‘Pasteur label’, and through maintaining a de facto monopoly in domains such as the production of anti-diphtheria sera. Besredka’s unorthodox approach, coupled with the production of his ‘antivirus’ by a large number of independent laboratories, might have been viewed as a threat to the institute’s ‘trade name’, and its dominant status in France as a producer of vaccines and sera. This difference, rather than purely theoretical disagreements, may account for the hostility exhibited by the Pasteur Institute towards Besredka’s endeavours.

Besredka’s main argument in favour of his ‘antivirus’ was that it worked. Antivirus, he explained, was successfully employed in the treatment of boils, cutaneous anthrax, infected burns, pyodermitis, carbuncles, sinusitis, otitis, cystitis, impetigo, acne, erysipelas, mastitis, eye infections and other chronic infections. The production of antivirus was undertaken by numerous small commercial laboratories in France and abroad. In addition, several more important pharmaceutical firms (Behring Werke, Institut Mérieux) also manufactured the antivirus. In all, thirty-three French laboratories and thirty-two foreign laboratories (in seventeen countries) commercialised the antivirus, under a great variety of trade names: Bouillon-vaccin, lysat, ampho-vaccin, aviril (sic!), propidex, staphydex, staly-sine, oravaccin, antigénine, enterophylaxine, parapayon, osmo-vaccin, creme séra-daussese, probios, ivago, microgel, gelo-vaccin, meta-vaccin, inosepta, antiflamin. In addition, pharmaceutical laboratories sold therapeutic products (‘sérobactéris’, ‘edwenil’) presented as derived from Besredka’s research. ‘There are few countries’, Besredka affirmed, ‘in which antivirus is not produced on a commercial scale. Judging from the prosperity of some of its production sites, there is probably a solid demand for this product’.

In 1932, Alexander Fleming, the head of the Inoculation Department at St. Mary’s Hospital, in charge of the production of vaccines for vaccine therapy, presented a new

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45 Besredka’s file in the Pasteur Institute archives contains correspondance between Besredka and laboratories that produced antivirus, and several letters in which Besredka protests against the use of his name in publicity for the anti-virus, probably as a answer to accusations made by the directors of the Pasteur Institute. For example, the directors of the firm ‘La Biotherapie’, one of the main producers of antivirus, wrote in 1936 to Besredka, to attest that they were shocked by the vicious, anonymous attacks on the honor of a man who never attempted to make profit from his inventions. Letter of C. Weisbrein, A. Alperine and A. Titoff, to Besredka, 8 October, 1936, Archives de l’Institut Pasteur, Besredka’s files, BES.1/2.
46 ‘Sérobacterin’, a therapeutic mixture of bacteria and antiserum was advertized in a leaflet, Mulford Working Bulletin, published by Mulford Laboratories, in 1926 and Edwenil, a substance isolated from blood of infected animals, was promoted in a booklet, ‘The endotoxic intoxications and their control with Edwenil’, published by Spitzer and Company in 1934.
47 Besredka’s memorandum to directors of the Pasteur Institute, undated (probably 1936 or 1937), Besredka’s file, Archives de l’Institut Pasteur.
therapeutic substance, the extract of the mould penicillium, stressing its resemblance to Besredka’s antivirus:

recently I have been making some observations on somewhat similar lines. I have found that when a particular mould has been grown in a broth for a week or ten days, the filtrate of the culture has remarkable inhibitory properties on the growth of pyogenic cocci. The filtrate, like Besredka antivirus, consists of nutrient broth, except that instead of being exhausted by a bacterium, it supports the growth of a mould for some time (not to exhaustion)... I have applied the filtrate to a number of septic wounds (abscesses, burns, ulcers, etc.) and so far the results are certainly not inferior to cases cited by Besredka... Penicillin may act in the same way as antivirus, but it is superior to ordinary antivirus in that it inhibits the growth of not only one but all pyogenic cocci.

In 1932, an older biotherapy—the ‘antivirus’—was both the model for a newer biotherapy—penicillin—and the standard for measuring the new preparation’s antibacterial activity.  

5. Vaccine therapy—the long and successful career of an ‘outmoded’ therapy

The anti-rabies vaccination can be accurately described as a ‘vaccine therapy’. It was, however, an exceptional case: vaccines were normally seen as a means of prevention, while specific antisera were usually regarded as cures. However, early in the twentieth century, the British bacteriologist Sir Almroth Wright proposed using vaccines to cure infectious diseases and, especially, chronic infections. His approach, grounded like the French biotherapy in a holistic perception of disease, combined the cellular view, developed by Metchnikoff, and the humoral one, promoted by the German school of immunology comprising Ehrlich and his followers. The articulation between these two approaches was made through the concept of ‘opsonisation’ (first proposed by Danysz and Leclef), which described the facilitation of phagocytosis of the pathogenic germs by specific antibodies in the serum. Wright elaborated a new therapeutic method, based on the vaccination of the patient by the infecting germ (either an ‘autogenous vaccine’ prepared with bacteria isolated from the patient, or else a ‘generic’ germ cultivated in the laboratory). The method—involving a long series of injections—shared many features with desensitisation treatment. Wright affirmed that his method was highly specific—each patient was to receive the treatment which was the most appropriate to her or his case. It was also, Wright claimed, a truly scientific approach, because the progress of the cure could be monitored through the evaluation of the ‘opsonin index’ of each patient—the quantitative evaluation of the phagocytic capacity of white blood cells measured in a test-tube.

Wright opened a highly successful ‘vaccination department’ at St. Mary’s hospital, where patients were treated mainly with autogenous vaccines. However, in some cases,

48 Fleming (1932). In 1929, Besredka gave a conference about antivirus at the Royal Society of Medicine, London (Besredka, 1929). On early history of penicillin see Hare (1970); MacFarlane (1984); Wainright (1990); Chen (1992).
49 Wright & Douglas (1903).
50 Danysz & Leclef (1895).
51 Wright (1909).
‘generic’ stock vaccines were seen as more appropriate as they were cheaper and could be administered immediately even when it was impossible to isolate the infecting bacterial strain. Vaccine therapy was highly popular before World War I, reaching its peak around 1910. It became codified in textbooks and presented as the latest development in the scientific treatment of bacterial infections. After the war, the therapy, which had many critics, was seen by many leading experts in bacteriology and immunology as outmoded and devoid of any scientific value. Medical practice is not, however, based purely upon scientific considerations. Although the scientific standing and prestige of vaccine therapy did decline from the mid 1910s, it continued to be widely used by patients and doctors, mainly because it offered a therapeutic possibility in diseases for which no other effective treatment existed before the advent of the sulfamides.

The main application of vaccinotherapy was similar to that of the ‘antivirus’: chronic infections. In such infections (and in pathologies ascribed to putative infections), the disease often follows an irregular course, with many ups and downs. Regression of symptoms could therefore easily be ascribed to the treatment, while temporary setbacks could be attributed to the need to fine tune the therapy and to adapt it better to the patient’s present immunological status. In addition, vaccine therapy—with its frequent subcutaneous injections and regular analyses of blood—could be seen as a combination of science-based medicine with an individualized treatment.

In the 1910s and 20s, several pharmaceutical laboratories produced bacterial strains employed in vaccine therapy. This therapy was, in fact, two distinct therapies (with possible intermediary variants). The treatment with autogenous vaccines was modelled on practices developed in Wright’s department at St. Mary’s. This was a therapy conducted exclusively by specialists who maintained a close relationship with the laboratory. The main steps were the isolation of an infecting germ from a patient, the preparation of an individualized vaccine, followed by long-term therapy with this vaccine, adjusted according to the results of repeated determinations of the ‘opsonic index’. By contrast, therapy with stock vaccines was close to routine drug therapy, and was regularly given by GPs without being linked to any ongoing laboratory analyses. In this case, laboratory analyses were only used for the initial identification of the infecting germ, and therapy with stock vaccines was possible even without any such identification. Some authors proposed always starting with a stock-vaccine therapy, and only switching to an autologous vaccine if it failed. The indications for such vaccine therapy were very broad, the most frequent being chronic infections such as boils and furuncles, acne, eye and ear infections, pyelonephritis or skin diseases. Moreover, vaccine therapy was employed in arthritis, sciatica, neuritis, rheumatic fever, rheumatism and goitre. The advocates of vaccine therapy explained that the underlying mechanism was the ‘stimulation of phagocytes’ (a concept that was later translated into the activation of the reticuloendothelial system, and then to the development of immunotherapies), or, alternatively, the neutralization of the ‘protein poisoning of bacteria’. The latter explanation is close to the ‘desensitisation’ of sensitised tissues,
and, indeed, indications for vaccine therapy were often similar to indications for the use of ‘anti-anaphylactic’ therapies.

In this same inter-war period, one of the most important indications for vaccine therapy was the treatment of rheumatism. In the late 1920s, a leading British expert on rheumatism, Warren Crowe, became an enthusiastic convert to vaccine therapy. Crowe recommended the use of stock vaccines to treat rheumatism (a polyvalent streptococcus vaccine and Micrococcus deformans vaccine). He suggested that these vaccines should initially be used at very low doses, with the amount of inoculated bacteria being gradually increased. The rationale behind this therapy was that individuals who suffer from rheumatism have a hidden source of infection, and that rheumatic symptoms were manifestations of a sensitisation due to bacterial compounds. Crowe and other authors explicitly linked arthritis to ‘hypersensitivity’, or ‘toxic idiopathy’: many arthritic patients, they stressed, also suffer from hypersensitivity to bacterial proteins, an element which needs to be taken into account when devising a vaccine therapy for arthritis. The Inoculation Department of St. Mary’s hospital, one of the main sites of elaboration of vaccine therapies, treated many arthritic patients. Rheumatism was however, only one among the numerous applications of therapeutic vaccines. In 1935, these included infectious diseases such as typhoid, paratyphoid, cholera, dysentery, the plague, pneumonia, influenza and whooping cough, as well as diseases directly attributed to bacteria such as acute and chronic rheumatic fever, acne vulgaris, furunculosis, or ulcerative colitis, and ‘idiosyncrasies’, such as asthma and hay fever.

St Mary’s Inoculation Department had close links with the firm Parke, Davis & Company, and Wright, Fleming and other workers at the Inoculation Department wrote the ‘vaccine therapy’ part of their catalogue. In 1935, Parke and Davis also issued a new edition of Wright’s Vaccine and serum therapy (first published in 1908), adding information about products manufactured by their firm and employed in vaccine therapies. Wright was initially an enthusiastic advocate of the use of individualized, autogenous vaccines and resisted the use of stock vaccines, a professional strategy that emphasized the bacteriologists’ unique expertise and skill. However, in 1935, he modified his point of view. Autogenous vaccines, he explained, are superior in principle, but in practice in many indications, such as furunculosis, erysipelas or acne, stock vaccines were as effective as autogenous ones. In addition, stock vaccines were cheaper, more readily available, and, above all, could be adequately tested and standardized. The 1935 study also explicitly linked vaccine therapy with desensitisation, especially in asthma and hay fever. Desensitisation, the authors proposed, may attenuate the pathological effects of infection, of sensitisation with bacterial proteins (the putative cause of rheumatic fever and of some allergic manifestations) and of sensitisation due to pollen or foodstuffs (‘toxic idio pathies’).

Reviewing recent developments in vaccine therapy in 1939, Fleming reiterated his faith in the future of vaccine therapy:

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56 Crowe (1930).
57 Ibid., pp. 41–47.
59 Fleming (1935).
60 Parke & Davis (1913, 1926).
61 Wright (1926).
62 Parke & Davis (1926), pp. 82–137.
at the present moment vaccine therapy is, in practice, having something of a setback in that medical practitioners have become chemically minded because of the sensational results obtained in certain infections by sulphanilamide and its allies. These drugs have an extraordinary effect on a small number of bacteria which infect the human body, and they are being used to treat all manner of bacterial infections whether or not there is any substantial evidence that there is a likelihood of their being successful. However it is certain that before long the limits of the new chemotherapy will be better understood, and I hope later to produce evidence that the best results in the treatment of certain bacterial infections will be obtained by a combination of vaccine therapy with the new chemotherapy.  

6. Treating allergies: specific versus non-specific therapies

Studies of desensitisation have a double origin: the work on the tolerance of gradually increasing doses of toxins, and investigations that linked the mechanism of immunity with anaphylaxis. Richet’s studies were grounded in the first approach, Besredka’s practical approach to desensitisation in anaphylaxis in the second. Besredka’s investigations into anaphylaxis aimed at the improvement of the safety of administration of therapeutic antisera. He experimented with the timing, dose and site of injection for sensitising substances, and was able to show that even animals with well established anaphylactic sensitivity can be ‘desensitised’ through intradermal injections of small doses of sensitising serum. On the basis of these experiments Besredka proposed that patients treated with antisera should be desensitised through prior intradermal injections of a small quantity of the same antiserum, a method he called ‘subintirant injections’.

Initially, Besredka proposed that anaphylactic shock was a rapid, uncontrolled desensitisation, a physico-chemical phenomenon that was not mediated by any specific chemical substances. Between 1908 and 1913, he temporarily adhered to the dominant view, which postulated that the reaction of sensitising substance with ‘antisensibilin’ led to the production of ‘anaphylotoxins’, which were regarded as being similar to peptones. As a consequence of this view, Besredka attempted to induce non-specific desensitisation using peptones. These attempts did not generate reproducible results, and in 1917 Besredka reverted to his original theory of anaphylaxis. Other researchers, among them Louis Pasteur’s grandson, Pasteur Vallery Radot, continued to pursue the path of non-specific treatments against anaphylaxis and allergy.

Vallery Radot, Widal’s student and collaborator, followed his teacher in combining an interest in physiology, bacteriology and anaphylaxis. In the 1920s, Vallery Radot became interested in allergy and anaphylaxis, and investigated these phenomena both in the lab-

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63 Fleming (1939). In July 1939, Fleming does not seem to have had an inkling as to what the next important therapy for infectious diseases would be.

64 Besredka & Steinhardt (1907); Besredka (1908, 1910).

65 Besredka (1908, 1909).

66 Besredka (1908).

67 Besredka & Ströbel (1911); Besredka, Ströbel, & Jupille (1913).

68 Besredka (1917).

oratory and in the clinic. He was familiar with physiologists’ studies of the mechanisms of anaphylaxis and, especially, with the studies made by Daly and his colleagues on the role of histamine. He attempted to reconcile the experimentalist’s vision of allergy with the ideas of Widal and his school concerning hemoclassic shock by making a distinction between the brutal and clear-cut anaphylactic shock observed in laboratory animals following a second injection of foreign protein, and the less dramatic although more complex allergic phenomena seen in the clinics. Anaphylactic shock induced by the injection of therapeutic serum was akin to the experimental phenomenon. By contrast, humans who suffer from allergies and have been sensitised in a gradual manner present a different set of clinical symptoms, termed the ‘colloidoclassic diathesis’, which reflect humoral perturbations. However, Vallery Radot added, these considerations are mainly of theoretical interest as physicians do not know how to re-establish humoral equilibriums. The best treatments for idiosyncrasies were either avoidance of the offending substance (if feasible), or else desensitisation.

When the cause of the sensitisation was unknown, a symptomatic treatment was proposed, consisting in either a drug therapy or a biotherapy. Among the drugs used to alleviate allergic symptoms were atropine, ephedrine (extract from the plant *Éphedra sinica*), belladonna, salicylates, dextrose, iodides, anaesthetic drugs and opiates. As I have already suggested, biological therapies were particularly popular during the inter-war period. The most popular among these therapies were gland extracts, above all adrenaline (used to reduce the symptoms of acute anaphylaxis), but also pituitin, thyroid extract and insulin. Other biological therapies included tuberculin (Van Leewens therapy), vaccinotherapy—either autogenous (with vaccines prepared from extracts of the patient’s colon bacteria) or heterogenous (stock vaccines)—injection of milk (proposed by Shiff) and other foreign proteins, autohemotherapy (advocated by the French), protein shock, and Witte’s peptone.

The last substance in this list was strongly recommended not only by Vallery Radot, but also by the British allergist Alexander Gunn Auld, who, in the 1930s, attempted to develop a scientific basis for the uses of peptone, especially in the treatment of asthma.

The status of non-specific biotherapies of allergies changed after World War II, with French physicians abandoning the ‘generalized theory of anaphylaxis’. The term ‘anaphylaxis’ became restricted to the rare cases of severe shock following injection of foreign substances or sensitisation by such things as insect stings, while the term ‘allergy’ was used only for pathologies such as asthma, urticaria, hay fever and skin reactions. Simultaneously, physicians gradually discarded non-specific biotherapies for allergic diseases, and proposed either specific desensitisation, or symptomatic therapies. Vallery Radot’s evolution is exemplary in this aspect. In the 1930s he continued to adhere to the holistic views propagated by the French clinical school. On the other hand, he frequently visited the USA, and was impressed by the attempt to make the study of allergies scientific

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70 Vallery Radot (1930). Desensitisation could be performed with commercial preparations. In 1926 Parke & Davis marketed 267 different protein extracts (mainly, but not exclusively, food extracts and pollens), sterilised and packed in collapsible tubes. Parke & Davis (1926), pp. 183–193.
71 Van Leewen (1925); Duke (1927); Oriel (1932); Feinberg (1934); Balayat (1936); Tuft (1937).
72 Auld (1936).
74 Vallery Radot (1937).
through the introduction of standardised and codified clinical practice. In the inter-war years, immunologists focused on the specificity and chemical structure of humoral antibodies, and developed precise, quantitative methods to measure antibody activity. At the same time, researchers interested in allergies failed to isolate the putative specific ‘sensibilins’ or to develop satisfactory animal models. They measured the skin reactions following exposure to poorly defined protein extracts, and relied on the subjective reports of patients. Accordingly, immunologists often viewed the study of allergies as a marginal, empirical domain. Vallery Radot and his colleagues believed that the gap between the study of allergies and other science-based medical disciplines could be bridged by making the clinical study of allergies more scientific and rigorous thanks to the standardisation of products, instruments and methods for making measurements.  

Another important element was the transformation of anti-histaminic compounds into drugs. In 1949, Vallery Radot’s textbook of allergic diseases still mentioned non-specific therapies, but its main subjects were specific desensitisations, and the use of anti-histaminic compounds, whose appearance was hailed as an especially promising development in the treatment of allergies. Similarities between the physiological effects of histamine and anaphylactic shock were described as early as 1911, but the participation of these substances in the clinical manifestations of allergy in humans was not established until the 1930s, and was only confirmed through the experimental and then clinical studies of the effects of the anti-histaminic compounds. It was, according to Vallery Radot, the description and then production of these anti-histaminic compounds that opened the way to the full integration of the study of allergies into the domain of scientific medicine. The main point, as Vallery Radot saw it, was not the intrinsic clinical value of these compounds (effective in the treatment of hay fever, but less so in case of more severe allergic manifestations) but the positive proof that allergies could be controlled by a well defined chemical substance with known physiological activity.

7. Conclusions: biotherapies in context

In 1932, the president of the French Medical Association, Fernand Besançon, explained that physicians had abandoned the notions of specificity and the etiologic period, and now focussed instead on physiopathological mechanisms. They were no longer expected to provide a specific medication for each disease, but rather drugs that acted on the modalities of reactions presented by the patient in various stages of the illness. This statement can be seen as a return to a physiological view of disease, which was popular in the nineteenth century. According to such a view, ‘diseases’ were artificial entities constructed by physicians mainly for didactic reasons. At the bedside, doctors did not deal with ‘rheumatism’, or ‘sepsis’ but with a unique set of symptoms and a unique individual. Accordingly, they were not aiming to provide a standardized treatment directed against the putative ‘etiolog-

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75 Worringer (1948); Vallery Radot (1962), pp.119–145.
76 These compounds were first studied in the therapeutic chemistry laboratory of the Pasteur Institute by Daniel Bovet and his collaborators (Bovet & Bovet-Nitti, 1948).
77 Vallery Radot (1949).
78 Dale (1952), pp. 199–211.
79 Besançon (1932), quoted by Mendelsohn (2001), p. 35. Besançon was a friend and collaborator of Vallery Radot, and a former student of Widal.
ical causes’, but were instead striving to control the major ‘disease moments’ experienced by the sick person.\textsuperscript{80}

The ‘Pasteurian sciences’ promised to put an end to ‘symptom-based medical thought’, and replace symptomatic therapies with treatments aiming at the elimination of the initial cause of the disease (often assumed to be infections). However, such specific treatments were slow to come, and in their absence physicians turned to any treatment able to attenuate the patient’s suffering and restore lost functions. The ‘sensitisation’ of tissues and organs by bacteria and bacterial products was viewed as one of the main intermediary links between an infection and its pathological manifestations.\textsuperscript{81} It also provided an effective bridge between new concepts derived from bacteriology and immunology, and the long tradition of pathological thought based on global notions such as ‘reactivity’.\textsuperscript{82} Therapies that attempted to neutralise the harmful effects of chronic infections through ‘desensitisation’ were not seen as marginal medical practices, but were promoted by leading advocates of the ‘Pasteurian sciences’, such as Richet, Widal, Vallery-Radot, Wright and Fleming. These physicians operated in the ‘no man’s land’ between the laboratory and the clinic, and proposed therapies that, because of their proximity to bedside tinkering, largely escaped homogenisation and regulation, even when the substances they used were produced and marketed on a relatively large scale.

Contemporary medicine continues to be driven by the search for the specific causes of diseases, and aims to develop specific means for eliminating these causes, a trend captured by the notion of ‘molecularisation’. In the inter-war era, non-specific biotherapies that aimed to fight ‘sensitisation’ were seen as lying at the cutting edge of medical progress. This view was radically modified following the development of antibiotics and hormonal therapies. After World War II, these non-specific desensitising therapies rapidly lost their legitimacy and were reclassified among the ineffective remedies, with any observed activity ascribed mainly to the placebo effect.\textsuperscript{83}

The majority of the biotherapies described in this paper—antivirus, haemotherapy, proteintherapy, peptones, and vaccine therapy—are found today only among ‘medical curiosas’ or ‘errors of the past’. A few others, such as the desensitisation of allergic subjects or specific immunotransfusion, are perceived mainly as a specific type of clinical practice. Only a few (glandular extracts, Penicillium broth) are viewed today as precursors of important therapeutic innovations. One could argue, however, that in 1930 it was very difficult to predict that the future of Fleming’s ‘penicillin extract’ would be radically different from that of Besredka’s ‘antivirus’, or that the antagonists of histamine would become an established cure for allergic phenomena, while Witte’s peptone, a popular treatment of the same condition, would be completely forgotten after World War II. The division between ‘true drugs’ and substances of uncertain status is possible only \textit{a posteriori}. In a biography of a drug, as in the biography of a person, a global judgement is possible only when we know the end of the story.\textsuperscript{84}


\textsuperscript{81} In 1935 Ludwik Fleck promoted a ‘colloidal’ perception of effects of infection with \textit{Treponema pallidum} (Fleck, 1979 [1935]).

\textsuperscript{82} Parnes (2003).

\textsuperscript{83} A fate that may await some of our present-day therapies as well. See for example David Healy’s criticism of new psychotropic drugs (Healy, 2001).

\textsuperscript{84} Goodman & Walsh (2001).
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