

THE ROMANTIC RATIONALIST A STUDY OF ELIE METCHNIKOFF

by

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TOWARDS the end of his life the tall, gaunt, stooping figure of Elie Metchnikoff (the French form of his name which he used for the last twenty-five years of his life) with long unkempt hair and flowing beard was almost a caricature of the Russian Bolshevik *émigré*. He might have stepped from the pages of a Dostoyevsky novel. His personality too seems to have combined the Rational and Romantic elements in a characteristically Russian manner.

Elie Metchnikoff was born on 16 May 1845, the fifth and last child in the family of a middle-aged, rather dissipated semi-retired army officer and an intelligent and beautiful woman of Jewish descent. The family name, Metchnikoff, was supposed to have been derived from a famous paternal ancestor, a Moldavian who was tutor to Peter the Great and Russian Ambassador to the Chinese Court in the seventeenth century. The ancestor's name was Nicholas Spatar Milescu, and Spatar, apparently meaning sword-bearer, was translated into the Russian word, Metchnikoff, by a nephew of Milescu.

The young Metchnikoff was a sensitive and emotionally labile child whose only strong attachment was to his mother. The strength of the bond between Elie and his mother is attested by the fact that he consulted her, until the time of her death, on every conceivable aspect of his life. It is tempting to attribute to this relationship Elie's manifest difficulties in adjusting to life as an adult man and his two extraordinary marriages.

The early years of Elie's life were spent in the feudal family estate in what is now the Eastern Ukraine. Left to himself in the midst of the overpowering steppe in which man took his place as a member of a closely integrated biological community and not as a manipulator of nature, Elie's interest turned early to natural history. At the age of six he used his pocket-money to bribe anyone he could find to listen to his lectures on the local flora and fauna.

When he was eight years old Elie came under the influence of a natural science student employed to teach his older brother Leo. Under the tutor's guidance Elie read voraciously in botany and zoology for three years and spent many hours collecting specimens of local plants and animals. In 1856 he left home and entered the *lycée* at Kharkoff. Here for the first time he encountered socialism, materialism and atheism. He clutched at the last like the proverbial drowning man at the straw. Another concept which made a big impression on him at this time was that the progress of civilization depended on the advancement of science. This notion became almost an *idée fixe* for him in later life. It was at Kharkoff, when he was fifteen years old, that Elie Metchnikoff first came across the world of microscopical biology. He was fascinated, and although Kharkoff University refused him access to a laboratory he borrowed a micro-

scope and took private lessons in histology. He wrote his first scientific paper at this time, but shortly after sending it off realized his observations had been incorrect and suppressed the paper. A year later he made himself thoroughly unpopular by publishing in the *Journal de Moscou* an adverse criticism of a geology book by a Kharkoff professor.

Elie finished at the *lycée* when he was seventeen, winning the gold medal in the final examinations. His mother persuaded him not to take up medicine and he decided to study biology instead. This was an exciting time for biologists. The *Origin of Species* had just been published, microscopy was in its infancy (haematoxylin was first used in 1863 and the microtome had yet to be invented), and the modern concept of the cell was slowly evolving. Many of the most important advances were being made in Germany, so it was to Würzburg that Elie made his way, to work with the great histologist Kölliker. Arriving in the middle of the long summer vacation, however, young Metchnikoff became so emotionally disturbed that he returned home and was left no option but to go to the local university at Kharkoff, where he entered the Natural Science Faculty. Less than a year later he published his first paper on the histology of Vorticella. This publication started the first of the many violent polemics which loomed so large in Elie's relationships with many scientists. He was unduly sensitive to any criticism, and criticism was much more forthright then than it is now.

He completed his university course in two years and moved on to work with Leuckart, the great taxonomist and parasitologist at Giessen. Here Elie had a most unfortunate experience. Some work he had done when Leuckart was away on holiday was published by the latter without Elie's consent and with no acknowledgement of him. Metchnikoff denounced Leuckart in a letter published in *Braune's und Du-Bois-Reymond's Archiv* and later gave a full account of the incident elsewhere.¹

Elie left Germany and joined his compatriot Kovalevsky at Naples. It was largely as a result of his association with Kovalevsky that he took up the study of embryology. A book published by Fritz Müller called *Für Darwin* impressed on Elie's mind the value of comparative studies. This book was a major piece of evidence in favour of Darwin's evolutionary theories and was seized upon by Haeckel as proof of his biogenetic law that ontogeny repeats phylogeny. The young Metchnikoff embarked immediately on a comparative study of the layers of marine invertebrate embryos. He looked for structural homologies and attempted to follow the fates of the cells comprising each layer. After several interruptions because of cholera outbreaks in Naples, Elie completed his work and wrote his degree thesis for Kharkoff University on the embryological morphology of the Cephalopoda, emphasizing the similarities between the early developmental stages of these and of vertebrates.

In 1867 Elie was awarded his degree and he and Kovalevsky shared the first Von Baer Prize for embryological research. In the autumn of this year Metchnikoff, aged twenty-two, was appointed Professor of Zoology at the new University of Odessa. After a few months, however, Elie had his first clash with authority, over university representation at an international congress, and resigned to take

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a post as professor at St. Petersburg. The job was offered to him largely as a result of the impression he made at the international congress at St. Petersburg in 1867. Before taking up his new post he travelled to Messina to work with Kovalevsky on invertebrate embryology again. Some conflicting results on the ascidian nervous system marred the friendship, and although Kovalevsky was eventually proved right things were never quite the same again. It was on arriving at St. Petersburg that Elie experienced the first of many attacks of depression. There was good reason for depression at this time as he had no facilities, no equipment and no heating, and his superiors turned a deaf ear to all his frenzied requests for help. In addition to this, he was so poor that he had to give evening lectures at the School of Mines to eke out his existence.

Elie became ill and was nursed back to health by a Mlle Fédorovitch for whom he soon conceived a considerable passion. She in turn fell ill with 'bronchitis' which became chronic. This alarmed Elie's mother but not Elie himself. By the time the marriage took place the bride was too weak and breathless to walk and had to be carried to church in a chair. Just before the wedding Elie wrote some illuminating letters to his mother. He says that speaking as an embryologist he intends to have no children and 'to preserve the utmost liberty', but also that he longs to have someone with him 'to whom I could become attached and who could share my pleasures and leisure'. The Metchnikoffs were so poor that Elie took to writing translations to earn extra money, and the only well-lit room in their flat was turned into a laboratory where he taught students every evening. His own research came to a standstill.

In 1869 the Metchnikoffs went to Italy, mainly because of Madame Metchnikoff's health. Here Elie wrote several papers which were illustrated by his wife. He applied unsuccessfully for a post in the Medical Faculty in St. Petersburg but was determined to leave the Zoology Department there. In 1872 he was appointed to the Faculty of Zoology at Odessa. On returning to Russia Madame Metchnikoff became much worse and Elie decided to take her to Madeira. To raise money, he wrote a paper entitled 'Education from the anthropological point of view' in which he put forth for the first time those views about the inherent disharmonies in human life which were to dominate his thoughts in later years. When they reached Madeira, Elie wrote another paper in the same vein called 'The time for marriage', in which he stressed the discrepancies between man's biological needs and the requirements of civilized life. At this time Elie considered giving up his job and opening a bookshop on Madeira, but was prevented by lack of money. He returned to Odessa to start his new job in the autumn of 1872. In January 1873 he was hurriedly recalled to Madeira where his wife was dying. On his arrival he heard that he had failed to obtain the Von Baer Prize he had expected, and a few days later his wife died. Elie broke down completely and attempted suicide on two occasions.

As his depression cleared he started to work. Because of trouble with his eyes he was unable to do much microscopy so he turned once more to anthropology and made two long, expensive and hazardous journeys to the Steppes of Astrakhan and Stavropol. He found the tribespeople very apathetic and attributed this to their habit of drinking fermented milk, believing this to lead

to chronic mild intoxication. He returned to this notion many years later, in a very different context.

It was on his return to Odessa at the age of thirty years that Elie's mind reverted to an earlier idea of finding a suitable young girl and training her for marriage. He selected the eldest daughter in a family of eight who lived in the flat above him and who had often annoyed him by the noise they made. He made his approach in a way which is almost too good to be true, by offering to give the girl private zoology lessons. Not unnaturally the girl's father did not take kindly to the idea of his daughter's serving an apprenticeship of some years before marriage, particularly to a man who was almost twice her age. He could not have been reassured by Elie's repeated remarks that he considered procreation a crime in a sentient being! However, the extraordinary match was at last arranged and in February 1875 Elie married for the second time. This time his bride was at least able to walk to the church, though she was afraid she would trip as her bridal gown was her first long dress.

Under her husband's expert tuition Madame Metchnikoff passed her final *lycée* examination shortly after her marriage. She seems to have regarded herself as utterly unworthy of her exalted husband and to have been completely dominated by him in every way. He on the other hand had this time obtained a perfect mother substitute who would never answer back and who was as clay in his hands. They both appear to have found this an eminently satisfactory arrangement and to have been very happy. His wife's main activity was painting, and though Elie was never really interested in the plastic arts he made valiant efforts to encourage his wife's attempts in this direction. His life was at this time filled by his work, his home and his friends, who were drawn exclusively from the staff of Odessa University.

Three years after his second marriage Elie's father died and his mother (now aged sixty-four and in poor health) and two of her grandchildren came to live with him and his wife. His mother did not live long, dying from a myocardial infarct. At this time his father-in-law made Elie the guardian of his children and so Elie and his wife acquired a 'family'.

For the next six years Elie Metchnikoff taught at Odessa University. It was a period of great political unrest and Elie's liberal views came to be regarded with suspicion. Eventually he realized that he would have either to resign or to give up his ideas of what a university ought to be. He chose the former course. During the intense emotional disturbance which accompanied these events, in addition to which he had to nurse his wife through a bad attack of typhoid fever in 1880, Elie again became severely depressed. For the third time in nine years he attempted suicide, this time he nearly succeeded! To prevent the stigma of suicide from casting its shadow over his family he inoculated himself with *Treponema recurrentis*. He was dangerously ill for some weeks but eventually recovered without any apparent sequelae.

It was at about this time that he first experienced 'cardiac trouble' (which might have been angina or merely effort syndrome). He consulted an eminent Viennese physician who found nothing wrong with him. It was also at about this time that Elie began to speculate on the origin of metazoa and became

particularly interested in the mechanism of digestion as a criterion of evolutionary development. After considerable experimentation he concluded that the intracellular digestion seen in planarians, some coelenterates, and echinoderms, was analogous to that in protozoa and was a primitive phenomenon. Even in those cases where a 'gut' was developed, mesodermal cells were responsible for the actual process of digestion which occurred intracellularly. He also started out to study the embryology of lower metazoa with a view to tracing pathways of evolution from protozoa. He coined the term Parenchymella for the stage in metazoan development at which he believed the endoderm was formed by the active inward migration of ectodermal cells which had become amoeboid and capable of digestion. He felt that this type of two-layered organism was a more likely candidate for the 'missing link' than Haeckel's gastraea in which the endoderm is formed by invagination of the single layered ectodermal blastula. He later produced a modified version of this hypothesis substituting the name Phagocytella for Parenchymella in order to emphasize the (to him) important fact that cells forming the endoderm were capable of ingesting and digesting food. An organism (the colonial choanoflagellate *Protospongia*) very similar to the hypothetical Phagocytella was discovered soon afterwards in 1880 by Saville Kent, and today the weight of embryological evidence favours Metchnikoff's view of the mechanism of formation of the endoderm, though the problem of the transition from protozoa to metazoa is still a matter for conjecture.

During the summer of 1879 at Naples and Messina, Elie continued his embryological studies and confirmed his earlier observation that among the mesodermal cells of many echinoderm and coelenterate larvae there were amoeboid cells capable of active intracellular digestion. The summer of 1880 was spent in Russia with his wife's family in the country where Elie made an attempt at the biological control of an insect pest. He infected beetles which were ravaging the cereal crops with a fungus he found growing on dead beetles. The experiments were unfortunately left incomplete, but they initiated Elie's interest in infectious diseases.

In 1881 Elie's father-in-law died and the next year his mother-in-law. This meant that he had to undertake the management of the family estates. Fortunately for him one of his brothers-in-law graduated from an agricultural college less than a year after he took over the job, and Elie was able to hand over to him. The money Elie inherited from his wife's family enabled him to give up his interest in his own parents' country property in favour of his brother's children and to be from this time onwards a man of independent means, an inestimable benefit to a person like him, and a fact that had a great influence on the course of his later work.

In the autumn of 1882 Elie, his wife, two of his wife's sisters, and three of her brothers, went to live in Messina as Elie longed to return to the Mediterranean, probably because of the happy associations the area had for him. They lived in a small flat with a sea view and a tiny garden. Living space must have been cramped as the drawing-room had to be turned into a laboratory. Here came what was probably the happiest time in Metchnikoff's life. For a whole year the 'family' lived at Messina with Elie pursuing his studies

on marine fauna and enjoying a good deal of leisure time—spent largely on sailing trips with local fishermen—with his wife and her young brothers and sisters. He was at this time endeavouring to trace the phylogenetic development of the digestive system and he became convinced that the mobile mesodermal cells of higher forms preserved the primitive intracellular digestive function to be observed in the similar cells of many lower metazoa and in protozoa. This idea was the core of his phagocytic theory, to which most of the rest of his working life—some twenty-five years—was to be devoted. It was at Messina that he first conceived the idea that the mobile mesodermal cells might play an important part in the ability of the organism to resist invasion by potential parasites of various sorts, an idea which was to turn him from zoology to pathology. The experiment he carried out of inserting a splinter in a transparent starfish larva has been described too often to need repetition here, but Elie was struck by the similarity between the ensuing reaction and inflammation in man and the higher animals. It is as well to remember that he was not the first person to observe phagocytosis, this honour is usually accorded to Haeckel's observations on the phagocytosis of indigo by the blood-cells of *Tethys* a gasteropod mollusc.² Neither was he the first person to suggest that the amoeboid phagocytic cells in higher animals might destroy bacteria they ingested, this having been done in a rather vague fashion by Panum in 1874 and Roser in 1881. It was Metchnikoff, however, who was undoubtedly responsible for the concept that phagocytic cells formed a defence mechanism within the metazoan body. He was the first person to stress³ that the wandering, and fixed, phagocytic cells of the metazoa were capable of digesting the bacteria they ingested and thereby protecting the body of which they were part. This was contrary to the views of most pathologists at the time who, although they recognized the fact that 'pus corpuscles' ingested bacteria, regarded this as deleterious, believing that the bacteria found a favourable environment within these cells which then merely served to disperse viable organisms throughout the body.

This 'phagocytic theory of immunity' for it was no less, unleashed a fierce argument, the echoes of which have yet to die out completely eighty years later! Two schools of immunology arose, the so-called cellular school led by Metchnikoff and supported by many eminent pathologists, among them Virchow, although many of those same histo-pathologists who had noted bacteria within 'pus cells' were violently opposed to the phagocytic theory. The opposing school of thought was the so-called humoral school led mainly by bacteriologists such as Buchner, Von Behring and Nuttall. In the view of this school the prime defence mechanism against bacterial invasion lay in the blood serum which could so easily be shown *in vitro* to be capable of lysing the bacteria.

The majority of the rest of Metchnikoff's working life was spent in attempting to minimize the part played in immunity to disease by humoral factors, and to establish beyond doubt that the phagocytic cells of the body were the decisive factor in this immunity. With remarkable tenacity and vigour he succeeded in meeting in a more or less satisfactory fashion each new threat to his theory, of which there were many.

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It was the work of Denys and Leclef in the 1890s and Almroth Wright and his collaborators in the early years of the twentieth century that first drew attention to the fact that both cellular and humoral mechanisms acting synergistically were vital for the resistance to infection of the metazoan body. They showed that for phagocytosis to occur satisfactorily in many if not all cases, serum factors which these workers called 'opsonins' were necessary.

The quality of Metchnikoff's observations and deductions on the resistance to infection of metazoa are easily assessed by looking at current views of immunity and comparing them with his. This was recently done for a number of concepts by Hirsch in 1959,⁴ and it is remarkable to see how few changes have occurred in many of the basic ideas during the intervening eighty years.

The two years of happiness at Messina were interrupted only by a retreat to the mountain village of Riva for the summer of 1883, and a trip to Odessa in the autumn of 1883 to attend a Congress of physicians and naturalists. In 1884 his wife and her eldest sister developed what appears to have been acute bronchitis and were advised to winter further south. Elie, his wife and his sister-in-law therefore set out for Spain, but being unable to find any congenial spot passed on to Gibraltar and, after a very stormy passage, to Tangiers. Elie, although he is said not to have had much taste for sightseeing, seems to have been very thorough in his tourism for he always read up the history, topography and art of the countries he traversed (and characteristically insisted that his wife did likewise) and hardly seems to have missed a single church, palace, museum, or art gallery in the length and breadth of Spain and Italy, no mean feat by any standards. Tangiers turned out to be intensely frustrating for him as the sea was virtually empty as far as littoral fauna were concerned, and he spent his time in going for walks with his wife and sister-in-law. The effect of the Tangiers climate on the latter was, however, remarkably beneficial and in the spring of 1885 they started back for Europe. They went first to Villefranche and then to Trieste, Elie working on various aspects of coelenterate and echinoderm embryology. In this same year, 1885, Metchnikoff was appointed Scientific Director of the newly founded Odessa Bacteriological Station which was established as a result of Pasteur's work with rabies vaccination. It was an institute devoted to the production and perfection of vaccines of various types. Alas for poor Elie, this, his last appointment in his native and beloved Russia, was destined to fail. The other members of the staff were medically qualified—a fact that Elie himself noted with some discomfort—and the local medical organization was very hostile to him and succeeded in manipulating the administrative section of the local government so as to interfere with his research. Violent disagreement broke out between members of the staff and Elie not being medically qualified was unable to carry out any human vaccinations himself, and so was utterly dependent upon his unfriendly assistants to carry out his programmes. Such a situation could not last and in 1886 he resigned and left Russia for the last time.

In 1887 Metchnikoff and his wife went to a Congress of Hygienists in Vienna. Here Elie made enquiries about a laboratory in which to work. Having tried

unsuccessfully one laboratory at Wiesbaden he decided to visit Pasteur. He was an admirer of Pasteur's scientific work and was delighted to find that the latter supported the phagocytic theory. At this time a new Pasteur Institute was being built in Paris, and Elie, seeing it was very large, asked if he might work there in an honorary capacity. Pasteur offered him a complete laboratory to himself. Thus, after twenty-five years of wandering through Europe, Elie was to settle in Paris until his death, a period of some twenty-nine years. Before finally accepting Pasteur's offer, however, since he was very worried at the prospect of living in a large city, Elie decided to look around further. After some unpleasant encounters in Koch's Institute in Berlin he returned to Paris to accept Pasteur's offer.

In October of 1888, therefore, a rather nervous Russian couple came to live in Paris. Part of their uneasiness was undoubtedly due to their having tried to get an impression of life in France by reading contemporary French literature. As this was the age of realism as expressed by Zola and others, their nervousness was understandable. However, they were relieved to find that the literary realism was rather lop-sided and soon settled into their new life. Metchnikoff had two rooms at the Institute and his wife acted as his assistant. Soon students, mostly young physicians, flocked to his laboratory and his 'empire' expanded until it filled a whole floor of the Institute.

In Paris and the Pasteur Institute Elie Metchnikoff seems at last to have found his niche. At first most of the other members of the scientific staff were opposed to the phagocytic theory considering it to be too vitalistic. They were gradually converted, however, and Elie's laboratory became the busiest and the most popular in the Institute, so that Elie himself often had to work at week-ends and during holidays as these were the only times he could get sufficient peace and quiet. He never refused to take on anyone who applied to work with him and thus had a constant and ever-increasing stream of students from all parts of Europe. He was from the beginning an ardent advocate of the policy of attracting people of unusual ability by paying them highly and of giving generous scholarships to young scientists starting out on a research career. In view of the fact that he himself was of independent means these were remarkable attitudes. Another facet of his progressive outlook was that he considered that the rapidly increasing complexity of biological research necessitated teamwork on the part of biological scientists. Throughout his life he devoted a considerable amount of time to the popularization of science. He wrote many popular articles, gave many public lectures, and was always ready to be interviewed by anyone concerned with the public dissemination of scientific knowledge.

During his years at the Pasteur Institute Metchnikoff took part in its teaching activities. These consisted of open courses of lectures, and right up to the end of his life Elie always prepared his lectures with meticulous care and always confessed to feeling terribly nervous for the first ten minutes of a lecture. As far as his students were concerned he was always generous with his time and knowledge and seems to have been a fairly tolerant master. However, with his somewhat obsessional personality and great emotional lability he was apt to

become quite violent with anyone whom he considered to be persisting in working along the 'wrong' lines or to be guilty of disloyalty.

For the first ten years of his life in Paris, Elie lived very close to his laboratory, moving out to the Sèvres district each summer. In 1898, however, he was enabled to buy a small villa at Sèvres with some money inherited from an aunt, and for the rest of his life he became that symbolic figure of twentieth-century urban life, a commuter. Like many such, he enjoyed the relative peace of life in an outer suburb and the possession of a garden; he also read a good deal during his daily train journeys to and from work.

In defence of his phagocytic theory Metchnikoff assiduously attended every European Congress he could and engaged in protracted polemics both verbal and written with his opponents. Early on he decided that the reason for the opposition to the theory among medical workers was that they were concerned mainly with pathological phenomena in man and higher animals. He therefore decided to investigate the comparative aspects of the inflammatory response, and in 1891, the year in which Cambridge conferred on him an honorary doctorate, he gave a series of lectures on the comparative aspect of inflammation which later became his well-known book *Leçons sur la Pathologie Comparée de l'Inflammation*.⁵ His thesis being that the main manifestations of inflammation—accumulation of blood serum and phagocytic cells at the site of the tissue damage—are seen throughout the metazoa, and that phagocytosis is a universal phenomenon in any inflammatory response.

It was about 1897–8 that Metchnikoff was struck by the fact that whilst polymorphs were very active in ingesting bacteria, macrophages tended to be more prominent in the phagocytosis of cells other than bacteria, including effete host cells. He then conceived the idea that senile atrophy of the human body might be due to phagocytosis by macrophages of host tissues altered in some way. This is probably the first recorded example of an 'auto-immune' process, at present so fashionable as a causal explanation of obscure diseases. Metchnikoff became more and more interested in the process of ageing and decided to finish his work on immunity and write a book containing his views so that he could commence work on the mechanism of ageing. The book, begun in 1899 and published in 1901, was his *L'Immunité dans les Maladies Infectieuses*,⁶ a work which, read against the background of present knowledge of immunity, seems naive in some ways but remarkably erudite in others, many of the questions asked so long ago being still unanswered.

Somewhere around the turn of the century Elie produced the notion that the cause of senility in general was a chronic intoxication due to the presence of 'putrefactive microbes' in the intestine. This idea has since become the touchstone of laxative manufacturers, advertising men and those people who are always ready to wash clean any part of the human anatomy no matter how inaccessible. It was first made public in the form of the Wilde Lecture which Elie gave at Manchester in 1901 entitled 'Flora of the human body'. At this time he put himself on a 'hygienic diet' which consisted of avoiding all uncooked food, as well as alcohol and tobacco.

His research on ageing was orientated in two main directions. First he

worked on the intestinal flora from the point of view of their possible role as a source of chronic intoxication, and then on the histology of those tissues which show prominent changes with increasing age, such as hair and skin. He seems to have convinced himself that macrophages were actively phagocytosing tissues in ageing animals, although probably in the case of hair he mistook melanocytes for macrophages containing pigment granules. These observations enabled him to account for senility on the basis of chronic intoxication and its weakening effect on the body cells which are thereupon phagocytosed by macrophages.

On this rather insecure foundation he built a vast psychological-philosophical theory of ageing in man. The essence of his attitude is contained in the book he published in 1903 entitled *Etudes sur le Nature Humaine*.⁷ He had by now become convinced that the physical changes associated with old age were abnormal and could be prevented by the application of science. One of his main reasons for this outlook was that he felt that the profound conflict, produced in humans, between impending death and the desire to live was 'unnatural'. For him all 'natural' behaviour was without conflict, after exertion one desires rest, after eating one feels full. His reason for the disharmonies present in man regarding old age was the presence of vestigial organs inherited from man's ancestors! He particularly incriminated the intestine, suggesting that the large bowel especially was a rather useless relic left over from the time when a faecal reservoir would have had survival value in allowing an animal to empty its bowel at a convenient time and not when being pursued. He appears to have entirely overlooked any possibly useful function of the large bowel such as water absorption. Elie suggested that if the usual premature senility could be prevented man would eventually come to desire death, and thus there would be no conflict. He suggested the name 'orthobiosis' for this 'normal' life-cycle for man, which he suggested would be of the order of one hundred and twenty to one hundred and thirty years. Much of his reasoning in arriving at these conclusions is quite extraordinary and shows little psychological insight. For instance, he suggested that the fact that very old people often desired to die supported his thesis that at the end of the orthobiotic cycle man would not dread death.

What measures did he propose to attain the orthobiotic state? The strengthening of the beneficent cells of the body (in some unspecified manner) and the transformation of the 'wild' (poisonous) intestinal flora into a cultivated flora by the introduction of useful and harmless microbes. He also laid stress on finding cures for infectious diseases, in particular syphilis, and on the prevention or cure of alcoholism. He was completely carried away by the idea that by applying the scientific method the nature of man could be moulded in any way that seemed desirable, a sort of brave new world. The closing sentence in the book on the nature of man gives us an idea of his passionate belief in the possibilities of science for good. 'And if it is true, as is so often affirmed, that it is impossible to live without faith, that faith must be faith in the power of science.' Sentiments similar to these though in a rather different context have been expressed more recently in a book by Bronowski.⁸ The majority of his critics at this time seized upon this book and pointed out that all the effort and

argument was merely devoted to postponing inevitable senile changes. This seems a rather unfair criticism but a large section of the public apparently accepted it. Nevertheless, in 1906 Elie was awarded the Copley Medal of the Royal Society for his researches in Zoology and Pathology.

Because arteriosclerosis is an almost invariable accompaniment of ageing, Elie decided to investigate this disease. Since syphilitic arterial disease was a well-known cause of arteriosclerosis, he was led on to an investigation of syphilis in apes and man. The work with apes was one of the early studies of the experimental disease in these animals. However, he dropped the work on syphilis after a fairly short time and returned to the intestinal flora. He published a book called *Essais Optimistes* in 1907 in which he reiterated his views on the poisonous nature of the large bowel flora. Some further bizarre arguments were presented to support these views, such as the fact that the shorter the intestine—and therefore as a consequence, the fewer the bacteria contained in it—the longer the relative duration of life! He quoted birds and bats as examples of relative longevity attributable to a short intestine. His philosophical treatment of the concept of death became more and more confused. He stated, for instance, that protozoa show no individual death, that trees have no 'inner' reason for their death which (he said) is due to external causes, and is therefore not 'natural'. Lower plants, however, were supposed to die naturally when their seeds were ripe. As many seeds are poisonous he suggested that the death of the plant might be due to auto-intoxication. He also mentioned that lactobacilli die in an excess of their own metabolic product, lactic acid, and included this as a further example of auto-intoxication to the point of suicide. He gave as examples of 'natural' death insects, the adult stages of which have an ephemeral life during which they are unable to eat owing to the rudimentary nature of their mouth parts. Why he should deduce from all this that 'natural' death was possible let alone desirable for human beings is very difficult to see. Even more difficult to comprehend is the concept that such a death would occur without causing any psychological distress if man completed his natural orthobiotic life-span. Why should a person in presumably good health be any more ready to die at one hundred and fifty years than at seventy-five years? He mixed a large amount of superficial psychology with his philosophical musings. For example, he suggested that pessimism (which he seems to have equated with depression) was prevalent in youth and optimism (which he equated with elation) in old age. Such statements being based as far as one can tell on his own personal experience of life, an analysis of Goethe's *Faust* as an autobiographical work, and the life-history of 'an intimate friend'!

At the time when Elie started his detailed work on the intestinal bacteria there were two opposing views on the subject. On the one hand it was held that the bacteria by their fermentative metabolic activity were essential to the process of digestion of food. On the other hand it was held that the bacterial flora of the intestine were not only unnecessary to the digestive process, but actively harmful to the organism by virtue of their production of toxic substances during metabolism.

As a start towards investigating the problem Elie studied the intestinal flora

(biota) of the bat. He apparently found only a very few bacteria, and this confirmed him in his belief that in birds and similar organisms with a relatively short gut, digestion could be carried out without the presence of micro-organisms. It was of course quite unreasonable to impute any role or the lack of it to biota in general just because they were or were not detectable in any particular set of experimental circumstances. Nevertheless, the findings in the bat, an animal with what Elie insisted was a relatively long life, encouraged him in his auto-intoxication theory. The fact that soon afterwards workers in France and elsewhere succeeded in attempts to rear 'germ-free' animals (as judged on the basis of the rather limited criteria then available) reinforced his belief that the biota were not essential.

Metchnikoff now set out to prove his auto-intoxication hypothesis, and was delighted to find amongst the biota several species of putrefactive micro-organisms such as the Clostridia which produced known toxic substances. With his collaborators Elie purported to have demonstrated that the toxic substances responsible for intestinal auto-intoxication were phenols and indols. They succeeded in producing artificial arteriosclerosis in animals by means of these substances, and also convinced themselves, if no one else, that other manifestations of senility were also produced by them. Having got this far Elie became sure that if the composition of the normal biota could be altered, all would be well. Knowing that many bacteria were sensitive to changes in pH when cultured *in vitro* he conceived the idea of changing the pH of the intestinal contents. To do this and also in the hope of 'seeding' the intestine with harmless bacteria he thought of using sour milk containing acid-producing lactobacilli. Further evidence on the potential usefulness of sour milk was the fact that, according to him, certain rural populations in Europe, for example in Bulgaria and the Russian Steppes bordering the Black Sea, who lived largely on sour milk were exceptionally long lived. Elie at this time introduced sour milk into his diet, the milk being prepared with pure strains of lactobacilli which he cultured himself. He also started regularly testing his urine for the presence of indol and phenol. He found his health benefited, so friends followed his example and physicians began prescribing the sour milk diet for their patients, such was Elie's scientific standing in the Paris of the time. This aspect later led to some unpleasantness. A Paris business man wanted to produce the sour milk on a commercial scale, and Elie was approached regarding the use of his name to sell the product. After consulting the Pasteur Institute's legal adviser he agreed to the advertising slogan 'Sole provider of Professor Metchnikoff'. Towards the end of 1912 when patriotic and nationalistic feelings were running high in Paris, Elie was accused of making a great deal of money from the sale of the sour milk. The charge though without foundation was hard to refute completely because of the slogan.

In 1908 Elie Metchnikoff was awarded the Nobel Prize for medicine and physiology—in recognition of his work on Immunity. The award was shared with Paul Ehrlich. In the spring of 1909 Metchnikoff and his wife travelled to Sweden to receive the prize, which he characteristically said had 'like a magic wand revealed to the public the value of my work'. He enjoyed the wild,

romantic Swedish landscape and the equally romantic Swedish paintings they saw. The Metchnikoffs travelled on to Russia, where Elie was received enthusiastically by the scientific world. They spent a day, which seems to have greatly impressed both him and his wife, at the country estate of Tolstoy. An interesting sidelight is that whilst both men liked the music of Beethoven, Mozart and Chopin, both found Wagner, and modern music, 'unintelligible, complicated and lacking in harmony'.

At this time Metchnikoff did some work on infantile cholera, the result of which incriminated *Bacillus proteus* as a causative agent. He also worked on experimental typhoid fever in anthropoid apes. At the same time he wrote a series of popular newspaper articles on the place of hygiene in the prevention of diseases such as typhoid fever.

In 1911 the Pasteur Institute financed an expedition to investigate tuberculosis in the tribes of the Kalmuk Steppes in South Russia. The expedition also intended to make a field investigation on the epidemiology of plague which was endemic in the Kirghiz Steppes. The Russian government sent a local mission to study plague along with the Pasteur Institute group.

The expedition appears to have been successful from all points of view. Positive tuberculin reactors were found to be least common in the more isolated parts of the region and to increase in numbers as civilization was approached. This seemed to confirm the idea that the high susceptibility of the Kalmuks was due to their lack of contact with the tubercle bacillus. Apart from some periods of physical discomfort whilst in the field, the members of the expedition were treated royally wherever they went. A period of five days travelling along the Volga by boat must have been one of the longest periods of complete relaxation in Metchnikoff's life. His own main impressions were of a considerable degeneration, both physical and spiritual amongst the Kalmuks, since his earlier visit in 1874. He attributed this to four main causes. The ravages of syphilis, alcoholism and tuberculosis, and oppression by the Russian administration.

After this expedition Elie returned once more to his studies of the biota. It was just after a break from this work in the autumn of 1913 that he experienced his first severe attack of left heart failure. On 19 October 1913 he had an attack of cardiac asthma which lasted for about six hours during which he made detailed notes of his sensations and emotions. He wrote 'I was thirsty and drank hot weak tea; I vomited; I felt wind in the stomach and the intestines' and 'undoubtedly my cardiac heredity is a bad one', and again 'It is possible that having very early begun an intense life, I have attained at sixty-eight a precocious satiety of living, just as certain women cease to menstruate earlier than the great majority.' Elie was back at work the day after these notes were written, but from this time onwards the slightest irregularity of his heart or gut was enough to make him seize pen and paper and write copious notes. A most illuminating note was made on 23 December 1913: 'During the past two months my health has been satisfactory, nevertheless I have wondered every day whether it would be my last.' He noted the appearance of the 'death instinct' in the following words, 'During my cardiac crisis in October 1913 I even felt no fear of death and my satisfaction at my recovery was less than before.' He was care-

ful to point out that since his had been an 'abnormally intense' life it was not surprising that he was ready to die at seventy years instead of the orthobiotic one hundred and thirty or so.

Metchnikoff's illness seems to have caused him to become rather depressed, as witness the note made later in December 1913, 'Scientific work still provokes in me an invincible enthusiasm, but I am becoming more indifferent to many of the pleasures of life.' Again in May 1914 he wrote that the music which had formerly moved him deeply no longer affected him and that the coming of springtime no longer gave him any feelings of elation. 'My predominant feeling is infinite anxiety for the health and happiness of those I love.' This depressive reaction to severe emotional stress was not new as we have seen, but Elie seems to have been more intellectually aware of it himself on this occasion.

As his dietetic requirements now precluded staying at hotels or boarding houses Elie and his wife used to rent a cottage at St. Léger-en-Yvelines for their holidays. In this cottage Elie managed to organize a small laboratory and thus was able to enjoy his holidays to the full. During the summer vacation of 1914 he started to study the silk moth as an example of an organism in which 'natural' death occurs, this moth having a life of twenty-five to thirty days and being incapable of feeding during this time owing to the rudimentary nature of its mouth parts. He was unable to find any obvious cause of death in the moths, but became convinced that their death was due to auto-intoxication, a result of the metabolism of their fat reserves which according to him produced toxins detectable in the excretions of the moths. These results, which Elie believed to be significant, added to his already unreasonable theory of auto-intoxication as a general phenomenon.

It was during the course of these experiments that he appears to have become obsessed by the idea of 'invisible microbes', micro-organisms too small to be seen with the microscopes in use at the time. This idea greatly worried him as he felt that a great deal of his work depended on the conclusive demonstration of the presence or absence of bacteria from a given situation.

The Declaration of War between Germany and France on 2 August 1914 ended the holiday and Elie's researches on the subject of 'natural' death. He received a bitter blow on his return to the Pasteur Institute, as, when he finally reached it after an heroic journey through a Paris disorganized by troop movements, it was to find it almost deserted. The Institute was under military command, most of the younger scientists had already left for active service, and all the experimental animals had been killed.

Being unable to do any practical work Elie started to write a book called *The Founders of Modern Medicine* in which biographical sketches of Pasteur, Lister and Koch were interwoven with his orthobiotic theories. In May 1915 the Institute celebrated his Jubilee and he characteristically wrote that the occasion touched him very much 'In spite of my distrust of sentimental manifestations, for I realized their sincerity.' He had by now completely adopted the comfortable philosophy that science would be the universal panacea and would alone enable men to live happy and full lives. He had also, he stated, now acquired a positive desire for complete annihilation at death, mainly it seems

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for the rather selfish reason that he could not bear the thought of being able in any after-life to witness the suffering of those left behind on earth.

In November 1916 Elie caught a cold. In December 1916 he had several severe attacks of cardiac asthma and eventually moved into a room in the Pasteur Institute to facilitate treatment. There, after frequent attacks of cardiac asthma, and an early right heart failure, he died at about 4.45 p.m. on 15 December 1916. One of the last sentences he uttered was to a friend, Dr. Salimbeni, 'You will do my post-mortem? Look at the intestines carefully for I think there is something there now.'

Thus ended the life of Elie Metchnikoff, the neurotic intelligent boy who became *l'enfant terrible* of biology, turned to a study of pathology mainly in order to answer criticism of his phagocytosis theory, won a Nobel Prize, and spent the rest of his life in search of the utopia of orthobiosis via the alimentary tract. A Rationalist, yes, but what an impossibly romantic one!

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REFERENCES

1. METCHNIKOFF, E., Entgegnung auf die Erwiderung des Her. Prof. Leuckart in Giessen, *Betreff der Frage über die Nematodenentwicklung*, Göttingen, Adalbert Rente, 1866.
2. HAECKEL, E. H., *Die Radiolarien*, Berlin, G. Reimer, 1862, p. 104.
3. METCHNIKOFF, E., Untersuchungen über die intracelluläre Verdauung bei wirbellosen Tieren, *Arb. zool. Inst. Univ. Wien*, 1883, 5, 141-168.
4. HIRSCH, J. G., Immunity to infectious diseases: review of some concepts of Metchnikoff, *Bact. rev.*, 1959, 23, 48-60.
5. METCHNIKOFF, E., *Lectures on the Comparative Pathology of Inflammation*, English translation by F. A. & E. H. Starling, London, Kegan Paul, Trench, Trubner & Co. Ltd., 1893.
6. — *Immunity in Infective Diseases*, English translation by F. G. Binnie, Cambridge, Cambridge University Press, 1905.
7. — *The Nature of Man: Studies in Optimistic Philosophy*, English translation by P. Chalmers Mitchell, London, Heinemann, 1903.
8. BRONOWSKI, J., *Science and Human Values*, London, Hutchinson, 1961.