Addison and the white corpuscles : an aspect of nineteenth-century biology / L. J. Rather.

Addison and the White Corpuscles

An Aspect of Nineteenth-Century Biology

L. J. RATHER

WILLIAM ADDISON (1802–1881) survives obscurely in histories of medicine today as a fore-runner of Cohnheim in describing the outward passage of white blood cells through the intact walls of small blood-vessels during the inflammatory process. Based on a thorough survey of relevant English, French and German medical and biological literature of the mid-nineteenth century, as well as on an analysis of all of Addison's writings, this book presents a quite different picture of his role. Addison was involved peripherally in two of the revolutions of biological science that took place in the nineteenth century, the first when the 'fibre' theory of plant and animal structure yielded to the cell theory as originally promulgated, and the second when the belief that animal cells arose *de novo* from an amorphous blastema yielded to the sweeping claim that all cells arose from pre-existing cells. These revolutions carried with them a necessity for re-thinking ideas of growth, regeneration and repair, and of nutritive, inflammatory and neoplastic processes. The white blood cells occupied a pivotal place in Addison's elaborately worked out physiological and pathological scheme of things. Now thought of as concerned solely with inflammatory and immune processes, the white blood cells had once been ascribed a role in tissue nutrition by German and French investigators. This view was adopted by Addison. In consequence he became one of the early adversaries of the 'blastema' theory of the origin of cells at

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. . . and now at the end of 1829, most medical practice was still strutting or shambling along the old paths, and there was still scientific work to be done which might have seemed a direct sequence of Bichat's. This great seer did not go beyond the consideration of the tissues as ultimate facts in the living organism, marking the limit of anatomical analysis; but it was open to another mind to say, have not all these structures some common basis from which they have all started, as your sarsnet, gauze, net, satin and velvet from the raw cocoon? Here would be another light as of oxy-hydrogen, showing the very grain of things, and revising all former explanations. Of this sequence to Bichat's work, already vibrating along many currents of the European mind, Lydgate was enamoured; he longed to demonstrate the more intimate relations of living structure, and help to define men's thoughts more accurately after the true order.

George Eliot, *Middlemarch*, 1871

We shall presently find that in science as well as in philosophy every period starts from certain assumptions and proceeds according to certain methods, that certain habits of thought become general, and certain views become accepted; but in the course of one or two generations we find those assumptions questioned, those methods criticised, a new habit of thought introduced, and those general views which seemed so natural and convenient giving way to new and altered ones. The whole fabric of society, the whole structure of science and knowledge, all the applications of art, have to be remodelled on new principles, and to meet our changed demands.

John Theodore Merz,
A History of European Thought in the Nineteenth Century,
4th ed., 1923, vol. 1, p. 56

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Preface

This book took origin as a lecture given in December 1969 at the Wellcome Institute of the History of Medicine in London. My topic was the supposedly long-overlooked discovery by William Addison—in 1843, more than two decades before Julius Cohnheim in 1867—that during the inflammatory process white blood cells passed through the intact walls of small blood-vessels into inflamed tissues. I found the story unexpectedly complex and interesting. Addison's so-called discovery cannot be detached from the body of his physiological and pathological theories without doing violence to his meaning. In turn, his theories can be understood only within the context of several important disputes that mark the course of mid-nineteenth-century anatomy, physiology and pathology.

Having far more material at my disposal than sufficed for a lecture, it occurred to me that a monograph on Addison fully exploring his involvement in the framework of mid-nineteenth-century medical and biological thought could at the same time shed needed light on some poorly understood aspects of that thought, and thus compensate for the fact that Addison himself was a relatively minor figure. In attempting to produce such a monograph it has also been my aim to avoid what has come to be increasingly recognized as one of the besetting sins of historians of medicine and science. That sin is to study past science not on its own terms but rather as if our present body of knowledge had absolute value. The historian who commits it reduces himself to the status of a special pleader for today's up-to-date textbook.

I am grateful to the Wellcome Trust for a fellowship granted me in 1969 to work in London on the history of the concept of inflammation, and to Stanford University for a half-year sabbatical leave during the same period. I wish to thank Dr. Noël Poynter, Director of the Wellcome

Institute of the History of Medicine, for both soliciting the lecture and encouraging me to write the monograph. Mrs. Lillian Robinett, Miss Mary Macias and Miss Joy Rowsey painstakingly prepared the typescript from the manuscript. The photographs for the plates were taken by Mr. Philip Horne. Plate 3, from Waller's paper, was prepared from a photograph lightly retouched under my direction by Mrs. Claire Mosely. Mrs. Jean Runciman added some final editorial touches and prepared the index. I am especially indebted to John B. Frerichs, M.D., for his editorial assistance in regard to the typescript and proofs.

Introduction

William Addison (1802–1881) was a medical practitioner of Malvern, physician to the Duchess of Kent and a Fellow of the Royal Society, a man whose publications on inflammation and nutrition made his name a familiar one in medical circles in the eighteen forties, both in England and abroad. His views on these subjects were in some ways novel and in others outmoded, but in both instances they clashed with the ruling dogmas of the time and were rejected, often harshly, by most of his contemporaries. Addison never occupied an academic position, but that he was by no means an outsider or mere eccentric is probably evident enough from his connexion with the Royal Society alone. Although the work that made his name familiar in England and on the continent was almost entirely done in the eighteen forties he was sufficiently well regarded a decade or so later to be given a Gulstonian Lectureship. According to his obituarist, Addison was compelled by reasons of ill-health to give up medical practice at an early age and retire to Brighton. It appears that Addison was to a certain extent a forgotten man in his later years. He is today at times confused with Thomas Addison (1793–1860), the great clinician of Guy's Hospital in London. Indeed, if we are to believe his obituarist, it was always true that he lived to some extent under the shadow of his greater (in the eyes of most) contemporary.[1]

Before giving the grounds for the survival of William Addison's name after his death it will be necessary to make a few preliminary remarks concerning the concept of inflammation, for it is within this context that such fame as he now has was achieved. Since the sixteenth century the word 'inflammation', or its cognates in other languages, has been in use as a technical term among Western physicians.[2] The *concept* of inflammation, on the other hand, has a much

longer history. (By concept I mean the events comprised under the heading of inflammation, hypotheses or theories regarding the means by which these events come about, and the so-called biological significance of these events.) It can in fact be traced back to the Hippocratic medical writings of classical Greece, although the first thorough synthetic view of the subject still available to us is no older than that offered by Galen in the second century A.D.[3] While the concept of inflammation did not play as great a role throughout the history of Western medical thought as some writers have claimed, it is nevertheless true that advances in anatomical, physiological or pathological knowledge, especially during the past three hundred years or so, have been reflected almost at once in the concept or concepts of inflammation dominant at the time. The reason is to be found in the fact that the concept of inflammation was, from the first, not merely a complex of signs and symptoms—the redness, heat, swelling and pain of Celsus in the first century A.D., so familiar to the readers of today's textbooks of pathology—but rather a theory of the way the body and its component parts 'worked' during a particular set of circumstances. Consequently the concept had to change whenever ideas of the structure and function of the body underwent change. Inflammation was always regarded as, in one way or another, the reflection of injury to the body, hence the concept was bound to undergo transformation along with changing ideas of the nature of injurious agencies. A very great change took place about ninety years ago (roughly coinciding with the death of William Addison) when the germ theory of disease began to win general acceptance and micro-organisms came to be seen as the chief agents of injury responsible for the inflammatory reaction. Our story takes place before that time, but we shall be led up to its threshold.

From the time of Erasistratus, early in the third century B.C., inflammation had been thought to be bound up in some way with events taking place in the vascular channels of the body. It was the opinion of Erasistratus that inflammation resulted when blood (which was thought to be normally

present in the veins only) forced its way into small arterial vessels designed for the transmission of 'spirit'.[4] Nearly five centuries later Galen disputed Erasistratus' premises and showed that during life blood is present in arteries as well as in veins. Galen's theory of the inflammatory process cannot occupy us here. We need only note that it emphasized the stasis or impaction of thick, viscid blood in small vessels as one of the essential features of inflammation.[5] When the so-called Galenic circulation of the blood—hardly a circulation at all in the proper sense—yielded in the early seventeenth century to William Harvey's discovery, the belief that stasis was at the bottom of the inflammatory process was found to fit in even better with the new Harveian circulation than with the old. As far as the theory of inflammation was concerned, the change from the Galenic to the Harveian circulation required only the substitution of a set of blocked tubules in a dynamic circulating system for the silted-up passages of a set of irrigation ditches.[6]

A good illustration of the influence exerted on the concept of inflammation by changed ideas of the workings of the body may be found in the writings of Franciscus de le Boë (1614–1672), or Sylvius as he is commonly known. Sylvius, who was professor of medicine at the University of Leyden, accepted the Harveian circulation and was at the same time an adherent of the new medical chemistry of his time. In his theory of the inflammatory process Sylvius attempted to weave in both strands of thought. And so he concludes that when the circulating blood stagnates in the veins or capillaries, or in the porous substance of the fleshy parts, it loses its more volatile and spirituous parts. Since the latter serve to temper the acid and saline components of the blood their absence leads to a reaction generating a 'warm effervescence' and in consequence the blood becomes 'inflamed'.[7]

Similar ideas were developed by other members of the iatrochemical school of thought. On the other side were members of the iatrophysical school, many of whom were of the opinion that chemical hypotheses need not be drawn on

to explain the workings of the body in health and disease. An example is Lorenzo Bellini (1643–1704), who regarded inflammation as the result of an impediment to the flow of blood brought about by mechanical obstruction, exsiccation of the blood or some such factor.[8] But while they were divided with respect to the validity of chemical hypotheses, both iatrochemists and iatrophysicists believed that the key, or at least one of the chief keys, to the understanding of the inflammatory process lay in the mechanisms controlling the circulation of the blood.

But how were the events of inflammation to be interpreted? What was their 'biological significance', in today's phrase? The question, then as now, is far too complex to allow for a simple answer. For the answer depends partly on the number and character of events included under the heading (or within the concept) of inflammation, partly on whether a conceptual separation has been made between inflammation as a unitary process and diseases in which inflammation is a prominent feature. In addition, medical opinion on these questions was neither uniform at any one time nor necessarily stable over longer periods of time. That the body had its means of self-therapy (of 'defence', as we now say) was an idea deeply rooted in Hippocratic medicine. Few physicians at any time since, whatever their persuasion, have doubted that an abscess, for example, represents a more or less successful attempt on the part of the body to discharge harmful matter. If abscess formation were regarded as an integral part of the inflammatory process then of course inflammation was, to that extent, a beneficial response on part of the body, rather than a disease *per se*. But what of the circulatory changes of acute inflammation? It is not until the appearance of Georg Ernst Stahl (1660–1734) on the scene that we find both an explicit affirmation of the value of the inflammatory process to the living organism combined with an interpretation, in this light, of the changes in blood flow.

Stahl was, he wrote, 'raised in the principles of Sylvius and Willis' at the University of Jena, where he studied medicine.[9] Although Stahl became the outstanding chemist

of his time he was unimpressed by the application of chemical science to the theory of human disease. He was more iatrophysicist than iatrochemist, although he did not believe that organisms were nothing but mechanisms.[10] As far as inflammation was concerned Stahl held, like most of his contemporaries, that its proximate physical cause was stasis or stagnation of blood in the affected part. The increased local heat was generated by the movement of blood through narrowed, partly obstructed, vascular channels. Redness and swelling were the consequence of an accumulation of blood in both the transmitting channels and the 'porous' parenchyma of the involved part (like Harvey, Stahl seems to have rejected the Galenic anastomoses supposedly connecting small arteries and veins, and knew of but rejected the capillaries as well).[11] Thus Stahl's presentation of what he calls the 'physico-mechanical rationale' of acute inflammation offers no particular novelty. His interpretation does, however, for he holds that the movements of the bodily parts concerned do not occur by virtue of mere mechanical necessity alone. Rather, they are subject to 'final' necessity, necessity determined by certain organismic ends or goals. The immediate physico-mechanical effect of the inflammatory process is the breaking up of circulatory stasis, but the 'mediate' effect (or end gained) is the preservation of the involved part from destruction. Gangrene or mortification of tissues, he points out, represents the failure of the inflammatory process to accomplish its task. Stahl emphasized repeatedly that while the inflammatory process brought with it certain inevitable inconveniences to the patient, these were nothing in comparison to the gravity of what would result did it not take place at all. Neither the physician nor the patient should allow himself to be misled or overly disturbed by these inconveniences. The heart of Stahl's idea, one clearly foreign to many physicians of his time and place, was that inflammation is a physiological 'action' on the part of the forces controlling the body, rather than a merely morbid or praeternatural 'passion'—in other words a reactive process rather than a disease or lesion.[12]

Throughout the eighteenth century opinions on the proper interpretation to be given to the inflammatory process (and thereby, to some extent, opinions on the proper treatment of inflammatory disease) remained at variance. Some physicians regarded inflammation as, in essence, a disorder of the circulation due to vascular derangement, a disease of small blood-vessels as it were. Others attempted to locate the source of the circulatory difficulty in the character of the blood itself. Still others, some of whom were followers of Stahlian ideas, saw inflammation as a physiological restorative process. The most important spokesman of this last viewpoint was John Hunter (1728–1793), the English surgeon and pathologist. Hunter included reparative processes under the heading of inflammation. He distinguished 'healthy' from 'unhealthy' varieties of inflammation but held that, in general, inflammation ought to be regarded not as a disease but as a healthy mode of reaction to disease. In his own words—words, incidentally, that reveal their Stahlian origin—inflammation is 'not to be considered as a disease, but as a salutary operation consequent either to some violence or some disease'. To this he appends the typically Stahlian comment that 'if a part under the influence of such irritation as should naturally excite inflammation had either no power or no disposition to exert them, the consequences would be much worse, for mortification would probably take place'.[13]

Although the visible changes occurring in small blood-vessels after irritation and injury were studied to some extent by Leeuwenhoek in the latter part of the seventeenth century, and in more detail by von Haller and Spallanzani in the mid-eighteenth century, it was not until a few years after the death of John Hunter that the microvascular features of the inflammatory process began to attract really widespread attention. The new and large wave of interest in the subject began its rise first in England and soon after reached the continent. The work of Wilson Philip along this line, beginning in 1799, was followed by that of John Thomson and Charles Hastings in the opening decades of the nine-

teenth century. In their wake came a host of investigators in Germany, together with a smaller number from France. By 1832 C. F. Koch could write an extensive review of the findings harvested by these microscopists, all of whom worked with the living blood-vessels of frogs, salamanders, fish, rabbits and other small animals. In Koch's review almost every finding—with one exception—now regarded as part of the inflammatory vascular reaction is described, in spite of the fact that most of the work antedated the introduction of corrected lenses. That one exception was the passage, during the course of the inflammatory process, of white blood corpuscles through the intact walls of small vessels into the extravascular tissues. As we shall see, the idea that blood corpuscles passed through in this way was by no means unfamiliar to investigators of the eighteen twenties and thirties. But none of them actually saw it take place, nor did most (if not all) of them distinguish between white corpuscles and red corpuscles in the circulating blood. René Dutrochet, whose name is frequently brought forward as one who, in 1824, observed the outward migration of white cells never did so in an unequivocal fashion, and he categorically denied his 'observation' in 1837. Increasing evidence that the capillary vessels had complete membraneous walls of their own and were not mere channels in the parenchymal tissues probably influenced him (as it did others) to abandon the theory that he had once upheld, namely that tissues were nourished by means of globules or corpuscles that passed from the bloodstream to the tissues and there became 'intercalated'. This 'intercalatory' theory, which had its proponents in England and Germany as well, was rapidly being superseded by the blastema theory. According to the latter the tissues were nourished by diffusion through membraneous vascular walls of a fibrin-containing proteinaceous matrix substance that constituted the non-corpuscular part of the circulating blood. The cell theory of Theodor Schwann, as set forth in 1839, fitted neatly into this scheme, since it maintained that 'cells' crystallized out of a blastema and subsequently underwent

transformation and development into the myriad structures of the body.

It is at this point in time that Addison enters the story. In 1840, his microscopic observations began to appear in print. They concerned the role of the white blood corpuscles in the formation of what was known as the 'inflammatory crust' (familiar to countless generations of wielders of the lancet in the blood drawn from their patients), the presence of increased numbers of white corpuscles in blood drawn from inflamed zones, and the changes visible under the microscope in the irritated small blood-vessels of the swimming-web of the frog. Addison picked up by then the almost entirely discarded 'intercalatory' or 'corpuscular' theory of tissue nutrition, changed it so that the white corpuscles and the white corpuscles alone were the elements concerned, and developed it somewhat along his own lines. Since at this time inflammation was rather widely regarded as in essence a derangement or heightening of the nutritive process, any new theory of nutrition almost necessarily involved a new theory of inflammation. Much of the present monograph is concerned with the development and decline of that aspect of Addison's work, and it will not be commented on further at this point.

The great wave of interest in the micro-vascular changes of inflammation subsided in mid-century. Addison's attempted revival of the intercalatory theory failed to win adherents and its rival, the blastema theory, was itself killed off in mid-century by Virchow's dictum, *omnis cellula a cellula*, all cells arise from other cells. In keeping with his attempt to explain all manifestations of the disease process in terms of disturbances of cells or groups of cells Virchow proposed an essentially cellular theory of inflammation. According to his view, inflammation was a cellular process set in motion by irritants, originating from within or from without, acting on cells. The initial response of the cell to the damage caused by the irritant was some form of degenerative breakdown. This was followed in due course by an increase in cell activity, manifested by changes in cell size,

number and other visible characteristics. Cellular changes involving increased activity on the part of the cells then led to an increased flow of blood to the part. Pus cells, for example, long known to be an integral feature of the local inflammatory process, arose (in Virchow's scheme of things) from the multiplication and transformation of connective tissue cells already present at the site of irritation. But Virchow's claim in this direction was soon to be challenged by his own pupil, Julius Cohnheim. In 1867, in Europe's leading journal of pathology, edited by Virchow himself, appeared Cohnheim's long and definitive study of the emigration of white blood cells through the intact walls of small blood-vessels at sites of inflammation, as seen in living frogs and rabbits.

Once again, William Addison's name arose, this time to begin its long journey through historical footnotes, editorial retrospects and biobibliographical notes down to the present time. For in a footnote to his paper of 1867, Cohnheim thanked Virchow for pointing out to him a passage bearing on his own work from a book by William Addison published in 1849. Cohnheim then quoted the passage verbatim in his footnote.[14] Cohnheim pays tribute to what he calls an 'exact and true observation', while at the same time discounting its 'strange' interpretation by Addison. On the basis of internal evidence it is obvious that Cohnheim had no real understanding of what Addison had done, for if he had he would not have called what Addison himself freely admitted was a necessary hypothesis, an 'exact and true observation'—assuming that Cohnheim's observation referred to the passage of white cells through the undamaged walls of small blood-vessels in the frog's tongue. As for Virchow, it seems relatively certain that at an earlier time he had understood the context of Addison's work and had known or suspected that the so-called 'exact and true observation' was merely hypothetical, since he had been one of those who actively opposed the claim that blood corpuscles ordinarily passed through vascular walls wherever it attempted once again to raise its head after its decline from

favour in the late thirties. In those days, certainly, he knew that the claim had at one time been given widespread acceptance. It also seems quite certain that in 1867 Virchow was as yet unacquainted with Waller's paper of 1846.

Since the time of its appearance in Cohnheim's footnote the name of William Addison has been periodically resurrected and honoured in one fashion or another, often with little or no understanding of what it was that he actually did or thought. Because one of the theses of the present monograph is that there exists a methodological reason to account for the prevalent misunderstanding of Addison's place in the history of mid-nineteenth-century medicine it will be necessary at this point to consider some of the assessments that have been made.

As we have seen there was a flaw in the very first of these assessments, that contained in Cohnheim's footnote, for here the context of Addison's work is passed off as 'strange' while his hypothesis—or, at the most, his very incomplete observation—is accepted as a precursor of Cohnheim's own observation. A few years later, in 1872, the passage from Addison quoted in Cohnheim's footnote appears (in the corrected version), in Cooper's *Dictionary of Practical Surgery*. The writer, who has just discussed Cohnheim's work in some detail, states that the passage from Addison seemed clear enough, and that the finding had been confirmed by Waller in 1846. But, he concludes, 'men's minds were not ready for the reception of these doctrines . . . and they were gradually forgotten by all save a few . . .'.[15] In 1881, the year of Addison's death, his obituarist in the *Medical Times and Gazette* (the vehicle of many of Addison's papers) wrote that Addison had lived 'before his time', and that the 'discoveries he made lay neglected until discovered long years after'. In particular, said the obituarist, Addison had anticipated 'in every particular' Cohnheim's showing that 'the white blood corpuscles inside the bloodvessels were likewise active, gathering together on the inner walls of the vessels, and then worming their way through to the tissues beyond'. He too quotes the same passage (corrected) from

Addison and, without mentioning the fact that it was to be found in Cohnheim's footnote, adds: 'Surely it would be hard to find a more accurate description than this of what are popularly supposed to be Cohnheim's original discoveries'.[16] In 1898 a new note was struck. Achille Monti, reviewing the historical steps toward the acquisition of pathological data, quotes the corrected passage from Addison, fails to mention (or does not know) that it first appeared in its original form in Cohnheim, and concludes that 'the merit, consequently, belongs to Addison of having formulated that doctrine which now unjustly passes under the name of Cohnheim'.[17] Dear to the hearts of some writers of the history of science is the 'forgotten man', the 'scientist who lived before his time', the patient worker in the vineyard whose efforts, now at last recognized, were for so long overlooked or misunderstood! Again, in 1907 Addison was accorded the sounding title of 'world's first great haematologist' by a writer in the *Lancet*. In this encomium Addison was given credit not only for having first described the outward passage of white cells (leucocytic diapedesis) but for having 'first discovered the meaning of the diapedesis of leucocytes in inflammation' as well. He was also said to have been the first to describe the blood platelets and the first to 'hint' at the presence of increased numbers of white cells in the blood (leucocytosis) as a concomitant of inflammation.[18] Finally, in the most recent (1968) collection of biographies of scientists Addison is awarded priority with respect to the description of both leucocytosis and leucocytic diapedesis.[19] It is my contention that these accounts are misleading where they are not simply incorrect, that they conceal from us Addison's actual accomplishments and his place in the context of mid-nineteenth-century medical thought, that they help to conceal the context of that thought itself, and that there is a methodological reason why this is so.

What is this methodological reason? To look back into the scientific past with an eye to the discernment of the who, when and where of a particular observation, hypothesis or theory regarded at the present time as valid is a legitimate

historical procedure. The working scientist himself often does this in the introductions to his papers. At the very least he will usually give a brief account of the relevant work of his contemporaries and immediate predecessors with whom he agrees or takes issue. Science is a co-operative endeavour in space and time, a continued conversation or argument extending over many generations, in the course of which scientists confront each other with arguments and evidence. But since the working scientist rarely finds it necessary to look back into the past for more than a few years or at the most decades, he finds it unnecessary to view what he sees with other than the customary schemata. He assumes, that is, a constancy of the framework, conceptual and factual, in which questions are posed, findings made and answers given. He has before his eyes a vision of an attainable, more or less absolute and non-historical, scientific truth. His interest is not primarily in what someone thought at some time in the past but in ascertaining what is (and always was and will be) actually the case. The historian of science, on the other hand, ought to be on the quest for the historical truth, the truth of how matters stood at a given time, of what happened, of what was actually thought and done. His primary business is not to correct the past or bring it up to date. Even if his ultimate interest is in setting up an account of the acquisition of still accepted hypotheses, theories or observational facts, he will never get off to a proper start if he insists on journeying into the past equipped with the prejudices and paraphernalia of modern science (whatever they may be at the time), uncritically fitting what he sees into the framework of the conceptions, preconceptions and prejudices of his own time. If he does so he will constantly be in danger of ignoring what does not fit in favour of what does, of seeing what he expects to see rather than what is before him, of discounting much of the evidence as unimportant and, finally, of distorting the past into an image of the present. The historian of medicine or science on a journey into the past ought to behave as an anthropologist rather than as a medical missionary.

Some concrete examples may be given where Addison himself is concerned. At the time when he is said to have given the first description of white cell diapedesis—the passage of white blood cells through the intact walls of capillaries and venules—he was in fact a strong proponent of the view that the smallest vascular channels had no distinct walls of their own. As did William Harvey, Georg Ernst Stahl, and many others after them, Addison thought that the ultimate vascular channels were like paths made by rivulets in the earth. As far as the outward passage of white blood cells is concerned, Addison was in one respect, perhaps, ahead of his time but in another distinctly behind it. Views similar to his own had been expressed by investigators in Germany, England and France as far back as two decades before he himself began to write on the subject. Accumulating evidence that the tiny vascular channels actually did have walls of their own led some men, such as René Dutrochet in France and Arthur Hassall in England to disavow their earlier views. Others did so tacitly or gradually. For example, in successive editions of the *Handbuch der Physiologie* during the eighteen thirties we can follow Johannes Müller's gradual abandonment of this doctrine.[20] The claim that Addison discovered the meaning of the diapedesis of white cells goes even further astray. Since the remark was made in 1907 our presumption is that the writer accepted the Mechnikovian account, i.e. the emigrated white cells were phagocytes on the hunt for invading bacteria. But Addison was, as has already been noted above, a somewhat belated modernizer of the corpuscular, 'intercalatory' theory of nutritive, growth and inflammatory processes. That theory had been replaced in the eighteen thirties and forties by the blastema theory, to which most of the leading French and German physiologists and pathologists of Addison's time gave their allegiance. Formative, nutritive and inflammatory processes were thought to be mediated by the passage outward from the bloodstream of a protein-containing fluid (chiefly composed of fibrin) into the tissues, where it was subsequently transformed into the solid

elements of structure, the cells and fibres. Addison, on the other hand, held that the white cells passed out of the smallest vascular channels, united with the tissues, and then underwent appropriate transformation. In this way he attempted to explain both normal and abnormal growth. At no time did Addison describe the actual passage of white cells from the vascular channels as an ongoing process—as Augustus Waller did, somewhat faultily, in 1846, and as Cohnheim was to do more accurately in 1867—rather he inferred that the passage must have taken place in order to account for his observations. As for the supposed description of leucocytosis, if this means an overall increase of white cells in the circulating blood Addison did not describe it—although others did at the time—and if it is taken to mean the local accumulation of white blood cells in small blood-vessels at sites of inflammation others had described it before him. Addison did point out that blood withdrawn from the base of a pimple or boil, or taken from the skin where a scarlatinal rash was present, contained many more than the usual small number of white corpuscles intermingled with the red.

The nature of scientific change. A notion of the feature of scientific work responsible for scientific change or progress usually determines the emphasis placed by an historian on all features of science taken together, for it is just this progress or change that attracts his attention in the first place. Currently there are two polar, but not mutually exclusive, views of the way in which science moves. According to the one, fresh, unprejudiced, objective observations, preferably quantitative rather than merely qualitative, of the 'facts' (which may, of course be elicited by experiment) bring us closer and closer to an understanding of things as they are, the objective natural world of which we are a part, a world that goes its way without regard for our desires or ends. According to the other, unprejudiced observation of the 'facts', must yield priority of place to something that becomes very plain once we study the actual procedure of the scientist (which is not necessarily what he says that procedure is or was),

namely, that in any developed science the scientist does not begin by writing his observations on a *tabula rasa* but first of all by accepting a body of traditional knowledge, then by choosing or being drawn to a problem or problem-area, and finally by making some new observations (or looking again at some older ones), in order to test them against received dogma (the inherited set of explanations, hypotheses, theories and presuppositions that constitute the body of his science). The scientist may be led thereby to introduce minor or major alterations in the fabric. In rare instances he reworks the whole pattern. More often his changes are minor, although they may not seem so, either to the scientist or his contemporaries, when first proposed. In retrospect their importance sometimes so greatly diminishes that we may be hard put to discern what was at issue, as if we were looking back at the work of tailors who had so concentrated the scope of their vision that they thought the fate of society contingent on the proper width of a lapel.

A multitude of intermediate positions connect the two poles. If we agree to call one the fact-oriented or observationist's pole and the other the theory-oriented or problematist's pole, the stance from which I write this essay is far closer to the theory-oriented pole. The nearer one moves to the other pole, the more fruitless it seems to busy oneself at all with the history of medicine or science. For if an observation be good or a fact valid it will be retained, if not it will be discarded. Why, then, rummage in the junk-pile of history? But, from the problematist's pole we see a host of men in each generation wrestling over and over again with an interrelated, organically growing and expanding set of problems. The pictures that they paint of reality—for they were just as certain as are we that they had grasped something of this reality—succeed each other like dissolving views projected on a screen by a magic lantern. It is as if we were watching a face with which we were quite unacquainted imperceptibly change by degrees to become the face of a familiar contemporary. But the dissolving views furnished us by history are not illusions, any more than is a

series of pictures connecting an infant with the man he becomes. It may be said that in the one case as in the other the well-springs of historical change have not been tapped. But my aim in this essay is only to follow the changes themselves, as they appear when one looks for a short distance backward along the path on which Western medicine has moved for the space of two and a half thousand years. Not a path that culminates only in *our* present, but one that has culminated in an infinite number of presents, each one as confident as our own that it had scaled the heights of time.

Bibliography and Notes

1. 'A forgotten chapter in the history of pathology', *Med. Times Gaz.*, 29 October 1881, p. 519.
2. Up until the end of the fifteenth century, and even to some extent thereafter, the Greek word *phlegmon* was commonly used instead of the Latin *inflammatio* as the generic technical term for inflammation in medical texts. Another generic term for inflammation, used by Guy de Chauliac in the fourteenth century, was the Greek *apostema*. Caelius Aurelianus, translating from the Greek into Latin in the fifth century, uses the term *tumor* for what we would today call inflammation.
3. Galen's ideas on inflammation (*phlegmonē*) are scattered throughout his voluminous works. The index to C. G. Kühn's edition is extremely valuable in this respect (*Claudii Galeni Opera Omnia*, Leipzig, 1821–33, 20 vols., Reprographischer Nachdruck, Hildesheim, 1964, 65). Important works of Galen on inflammation available in modern languages are Charles Daremberg's *Œuvres anatomiques, physiologiques et médicales de Galien*, 2 vols., Paris, 1856; cf. vol. 2, pp. 745–84; and Galenos, *Ueber die krankhaften Geschwuelste*, translated and introduced by Paul Richter, Leipzig 1913, series *Klassiker der Medizin*.
4. According to Celsus, if 'sanguis in eas venas quae spiritui accommodatae sunt, transfunditur' the result is 'inflammationem, quam Graeci *phlegmonēn* nominant' (Celsus, *De Medicina*, 2 vols., London, 1948, vol. 1, pp. 9, 11).
5. Galen, ed. Kühn, op. cit., vol. VII, *De differentiis febrium*, lib. ii., p. 375.
6. John G. Curtis pointed out that Galen followed the example of Aristotle and Plato in comparing the function of veins to that of irrigation ditches (*Harvey's Views On the Use and of the Circulation of the Blood*, New York, 1915, p. 8).
7. Sylvius, *Opera Omnia*, Amsterdam, 1680, cf. *Praxeos medicae*, lib. l., pp. 281, 282.

8. Lorenzo Bellini, *De urinis et pulsibus, de missione sanguinis, de febribus . . . dicatum Francisco Redi*, Frankfurt, 1698; cf. *De missione sanguinis*, pp. 121, 122.
9. Georg Ernst Stahl, letter to L. Schroeck, cited by Albert Lemoine, *Le Vitalisme et l'Animisme de Stahl*, Paris, 1864, pp. 33, 34.
10. L. J. Rather, 'G. E. Stahl's psychological physiology', *Bull. Hist. Med.*, 1961, **35**, 37–49.
11. Georg Ernst Stahl, *Theoria medica vera*, edited by Ludwig Choulant, 3 vols., Leipzig, 1831–33; cf. vol. 1, pp. 252–64. Stahl states here that certain 'speculators' have denied the existence of the pores and have asserted that blood remains within vessels, albeit very fine ones, throughout its circuit. He was by no means the only one who regarded this opinion as speculative. It is interesting to note that Stahl's contemporary, Archibald Pitcairn, who did reach the conclusion that a porous interstitium could not possibly intervene between the terminal branches of the arteries and the beginnings of the veins, reached it on *a priori* mathematical grounds (*Opuscula medica*, Rotterdam, 1714; cf. *De circulatione sanguinis per vasa minima*, pp. 31, 32).
12. Stahl, op. cit., vol. 2, pp. 219–23. Stahl even wrote a short poem on the topic, in his role as *praeses* over L. J. Walter's inaugural dissertation *De inflammationis vera pathologia*, Halle/Magdeburg, 1705. The key lines, in which Stahl reproaches both physician and patient for misconstruing Nature's healing efforts, are:

    Sed laudant Medici sua pharmaca, quamlibet aegros
    Dum sanant, angant saepe dolore gravi.
    Quae tanta invidia est, ut quod Natura saluti
    Consulit, hoc Medicus damnet et aeger idem:

    The physician's role is, however, not merely that of a passive onlooker. He may have to restrain Vesta, so that her fire does not become lethal. This admonition is found in another poem appended to Walter's dissertation, offered by J. C. Fritsch:

    Ignes nosse bonum est, inflammatosque recessus,
    Cum Medicam anhelans postulat aeger opem.
    Tu Vestam salubri freno moderabere, ne qua
    Vel rosa, vel tristi purpura flore necet.
13. The most useful edition of Hunter for the purposes of the present work is that edited with notes by James F. Palmer, *A Treatise on Blood, Inflammation and Gun-Shot Wounds*, Philadelphia, 1840. Cf. pp. 285, 286, including Palmer's footnote remarking that Hunter's distinction involves 'too great refinement'. See also Ch. III.2, note 26.
14. Julius Cohnheim, 'Ueber Entzündung und Eiterung', *Arch. path. Anat., Physiol. klin. Med.*, 1867, **40**, 1–79. See Ch. II.6 for the passage as it appeared in Addison's book. Cohnheim quoted the passage verbatim. Other writers, beginning with the obituarist in the *Medical Times and Gazette*, loc. cit., 1881, make the necessary correction by inserting a

'more' that had clearly fallen out of one of Addison's sentences. The only other name mentioned by Cohnheim in this connexion is that of Zimmermann, who, he writes, claimed in 1852 that all cells present in inflammatory exudates were by origin white blood cells. But Zimmermann's claim, according to Cohnheim, rested on hypothesis alone. Why Cohnheim used the comparatively late date of 1852 is not clear, for Zimmermann's hypothesis was put forward long before that time. In an article published in 1847 Virchow referred to Zimmermann's espousal of the hypothesis as one of several years' standing. Interestingly enough, Virchow at that time allowed for the passage of a few red and white corpuscles from the bloodstream to the tissues during inflammation. 'We know,' he writes, 'that during inflammation red as well as colourless corpuscles often pass out, but that nothing develops from them, instead they retrogress and succumb.' (*Herr Dr. Zimmermann und der Eiter, Literarische Beilage zur med. Zeitung*, V/9, September 1847.)

15. Cooper's *Dictionary of Practical Surgery and Encyclopaedia of Surgical Science*, 2 vols., London, 1872, vol. 2, article 'Inflammation', by R. Druitt, p. 72.
16. *Med. Times Gaz.*, loc. cit. The writer states that up to the present time, i.e., 1881, 'Virchow's notion had been generally accepted that the connective tissue cells or fixed corpuscles were the chief agents concerned in multiplying, under irritation, and with a due supply of nutritive material, so as to create heaps of pus corpuscles or other new formations, and that the blood vessels simply served as a means for conveying an increased quantity of nutrient elements to the part'. The remark is somewhat misleading, for Virchow's ideas on the subject did not receive widespread acceptance until some time after the publication of his *Cellularpathologie* in 1858. Even then many dissenters remained (see Appendix C). The obituarist states also that while Addison had expressed some of his views in 1841 and 1843 'it was not until 1849, after Waller's experiments had been made public . . . that Dr. Addison, in a new work on Healthy and Diseased Structure, was able to formulate his doctrines clearly and precisely'. The implication here that Addison knew of Waller's paper is plain, but I have not been able to find any other evidence that he in fact did.
17. Achille Monti, *The Fundamental Data of Modern Pathology*, trans. from the Italian by John Joseph Eyre, London, 1900, p. 36.
18. Hugh A. McCallum, 'William Addison, M.D., the world's first haematologist', *Lancet*, 1907, i, 182–83. McCallum's generous tribute is unfortunately a compendium of errors. Among other things he claims that Addison was the first to recognize the leucocyte as a separate blood cell in man and the mammals. The article also says nothing of the theoretical context in which Addison placed his observations.
19. *World Who's Who in Science: A Biographical Dictionary of Notable Scientists from Antiquity to the Present*, ed. by Allen G. Debus, Chicago,

1968. The note reads: 'Gave 1st known description of leukocytosis (under another name), also credited with 1st identification of diapedesis.' Garrison and Morton's *Medical Bibliography* (2nd ed., New York, 1954), p. 267, cites the *Lancet* article of 1907 and credits Addison with the first description of leucocytosis and the first observation of diapedesis. Addison is also said to have 'anticipated Cohnheim's conception of inflammation', thus further compounding the confusion. The *Biographisches Lexikon der hervorragenden Aerzte*, Nachtraege zu den Baenden I–V (3rd unchanged ed., Munich–Berlin, 1962) cites both the *Lancet* article of 1907 and the *Medical Times and Gazette* article of 1881 but states that Addison 'beobachtete die Auswanderungen der roten [*sic*] Blutkoerperchen' (p. 11).

20 Cf. Ch. II/1, p. 63.

I The Era of the Blastema

I.1 Addison on the White Corpuscles and the "Buffy Coat"

In his first communication to the *London Medical Gazette*, dated 10 December 1840, William Addison described a series of events, seen in blood drawn for therapeutic purposes, that must have been quite familiar to most, if not all, of his audience. When blood was withdrawn from the arm of a healthy person, wrote Addison, it solidified or coagulated within five or ten minutes into a homogeneous, reddish, jelly-like mass. If it were left standing in the container a clot (defined by Addison as coagulum free from serum) would begin to separate from the sides. After eighteen to twenty-four hours of contraction the clot appeared as a dark red, homogeneous mass bordered and overlaid by clear straw-coloured fluid, the serum. The clot, Addison stated, was generally thought to consist of 'fibrine' and red blood globules. So much for the normal course of events. In persons suffering from acute rheumatic or other inflammatory diseases the course was otherwise. During the few minutes before coagulation took place the surface of the drawn blood in the physician's basin might show a curdled or flocculent appearance, it might be 'patched with purple or buff' or it might be overlaid with so thick a layer of yellowish-white fluid as to obscure the red beneath. And the clot subsequently formed would no longer be homogeneous. Its lowermost and larger portion would be red, as before, but the upper layer would consist of a yellowish-white or buff-coloured mass, called the inflammatory crust or buffy coat. In some instances the surface of the buffy coat would become 'cupped' or indented.[1]

Countless generations of physicians had used the procedure of bleeding for both diagnostic and therapeutic purposes, and there was nothing new to be found in Addison's description of the inflammatory crust, as so far given. A contemporary encyclopaedia of medicine, published in London in 1833, states that aside from its presence in blood drawn from patients with severe inflammatory or febrile disease the buffy coat might be observed in pregnant women, in individuals in 'a state of sanguineous plethora', and in patients in the habit of being bled often. The buffy coat indicated actual inflammation or a predisposition to it, but the degree of buffiness was not proportional to the severity of the inflammation. There was a thicker buffy coat to be seen in connexion with inflammation of the fibrous tissues, as compared with inflammation of the internal organs. Sometimes the coat was absent, as in subacute inflammations, in 'phlegmatic' subjects and in 'typhoid' fevers. Its immediate cause was subsidence or settling out of the red globules before coagulation was complete. But it was not due to delayed coagulation alone, since coagulation sometimes occurred more rapidly in 'inflamed' than in normal blood.[2]

Addison then proceeded to report some observations that he considered to be novel. After taking sixteen ounces of blood from a man ill with pleuritis Addison found that he could draw off the upper buff-coloured layer before it coagulated. This procedure yielded two fluids, one buff coloured and the other red; both subsequently coagulated and then separated into clot and serum as before. Repeating this procedure in a patient with acute rheumatism Addison transferred a drop of the buff-coloured fluid to a glass slide and examined it with a Coddington lens.[3] He saw a large number of colourless globules, which he took to be lymph globules or red globules freed of their colouring matter. He concluded that inflammatory or buffy blood had 'two kinds of globules; the heavier red globule sinking to the bottom, and forming the lower portion of the clot, and the colourless lighter globules swimming at the top'.[4]

Although he does not say so explicitly, Addison seems to have supposed that some of the colourless globules were not pre-existent in the overlying fluid. They 'developed' in the fluid, he wrote. The sole authority whom he cites in his first paper, Johannes Müller, is credited with the belief, evidently considered incorrect by Addison, that the fibrin of the blood is present in a dissolved rather than a globular form. Nor does Müller, Addison points out, have anything to say of the participation of white globules in the formation of the buffy coat.[5] What Addison regarded as new was his showing of the large number of white globules or lymph corpuscles in the still fluid upper layer of rapidly sedimenting blood drawn from patients with inflammatory disease, and their participation in the developing inflammatory crust or buffy coat. The reader must bear in mind that the 'buffy coat' seen by the modern haematologist in blood treated with an anti-coagulant and then centrifuged consists almost entirely of white blood cells, whereas the buffy coat or inflammatory crust of the older physicians was a mixture of fibrin, white blood cells and other plasma components. The buffy coat of the modern haematologist (who rarely uses the term) is present in more or less degree as long as any white cells are present, whereas the buffy coat of the older physicians appeared only when sedimentation of the red blood cells took place to an appreciable degree before coagulation occurred.

Addison's next communication to the *London Medical Gazette* was dated 12 January 1841.[6] After describing once again the manner of formation of the buffy coat or inflammatory crust in human blood and noting that the colourless globules 'become more numerous' in the upper layer of the settling blood, he shifts abruptly to a description of the capillary circulation as seen under the microscope in the swimming-web of the frog's foot. By 'capillaries' he understands channels just large enough to allow the passage of red globules in single file. In addition to the familiar red globules, which he now describes as bodies with 'flat faces', Addison describes slightly smaller, rounded globules marked

with 'little specks or spots'. These he considers to be 'lymph globules' and similar to those present in such large numbers in human blood under the conditions already described. After placing a particle of salt on the web Addison observed the stream of blood in the capillaries to be at first retarded and then accelerated. Two days later the web appeared to be inflamed, i.e. it was discoloured by reddish streaks. Under the microscope a great number of the lymph globules were now seen to have accumulated at the periphery of the capillary and small venous channels. Some were stationary, others were slowly urged along by the passing stream of red globules. When inflammation is excited, writes Addison, 'more lymph globules are developed'.[7] This ambiguous statement leaves it unclear in our minds, as it doubtless was in Addison's as well, how many of the lymph globules were brought to the site of the inflammatory process and there deposited, and how many were 'developed' on the spot.

The third communication of Addison to the *London Medical Gazette* is dated 14 March 1841.[8] In spite of its title we learn from it nothing more about the white globules of the blood. Addison states specifically that the red globules are confined to the vascular channels and their function, 'whatever it may be, whether in aiding the endosmosis of the several secretions, or keeping the fibrin fluid, is confined to the blood; they have nothing to do out of the blood-vessels'. We are not told whether the white globules have anything to do out of the blood-vessels. Clearly Addison has not yet conceived the idea and made the observations that will later convince him that the white globules do in fact pass from the bloodstream to the tissues. He has not yet conceived his corpuscular theory of nutrition (of which more later), for he states that the circulating blood contains in solution a peculiar substance, fibrin, capable of constituting solid organized tissue after 'a moment's rest'. Fibrin formed the staple material of the elastic tissues, of muscular fibre, of cellular tissues (i.e. connective tissues, not tissues composed of cells) and of blood-vessels; it was the 'connecting

link between the solids and the fluids'. These remarks seem to imply that fibrin passed out from the bloodstream in dissolved form into the tissues where, once it came to rest, it was transformed into the various solid elements of the tissues. If this was Addison's implication his views did not, at this time, differ from those of most of his colleagues in the medical sciences. All normal structure, he says, is built up by the capillaries (which are 'minute fibrinous canals'), fibrin and albumen. The albumen remains in solution when it leaves the vascular channels, but the fibrin solidifies at once. At a time when the ultimate structural unit of the tissues was the 'fibre' rather than the 'cell' as was the case almost up to the end of the first quarter of the nineteenth century, the coagulation of the fibrin contained in drawn blood into a semi-solid, stringy, 'fibrous' mass seemed a plausible model for what happened when this same fibrin, possibly together with other proteinaceous material, passed beyond the blood channels into the interstices of the tissues. The increasing recognition accorded to cells in the eighteen thirties by investigators of plant and animal structure, culminating as far as the latter were concerned in Theodor Schwann's book of 1839, did not alter matters for the cell simply took the place formerly occupied by the 'fibre' as the primary unit of solid structure, formed from a proteinaceous fluid present in largest quantity in the circulating blood, whence it was distributed to the tissues. This formative or plastic substance, the coagulable lymph of late eighteenth-century writers, was now termed the 'blastema'.[9] It is important that we keep these facts in mind, for Addison was soon to become the proponent of an alternative theory of the way in which tissues were nourished by the blood, and in this theory the role of the white blood cells and their passage from the capillary channels into the tissues is crucial.

So far Addison's work had gone apparently unnoticed. But in 1842 there appeared a review article by T. Wharton Jones on the anatomy, physiology and pathology of the blood, critical of Addison on two points. Firstly, wrote Jones, Addison incorrectly supposed that the buffy coat of

inflammatory blood was formed by the coalescence of colourless corpuscles. Secondly, Addison seemed unaware that the existence of colourless corpuscles in the buffy coat was 'no new observation'. The truth of the matter, according to Jones, was that when the fibrin of the fluid part of the blood coagulated to form the buffy coat the colourless corpuscles became entangled among the 'fibres and minute granules into which the fibrin solidifies'.[10] To these remarks Addison replied, later in the same year, that his words in the article cited by Jones had been 'coagulation takes place by the thickening of the film and the firm aggregation of the globules'.[11] He refused to see the ambiguity of this statement which, if anything, adds substance to Jones' adverse criticism. Addison then refers to another paper in his series published, he says, six months before the appearance of Jones' observations. Here, it is true, Addison states that fibrinous filaments begin to form in the coagulating buffy coat, increase in number, cross and interlace, and thus come to enclose and draw together the colourless corpuscles.[12]

Addison's last-mentioned paper is of interest on several further counts. Examining the blood and muco-purulent sputum of a young woman with pulmonary disease Addison became aware of numerous, minute 'molecules or granules' averaging about one-tenth the diameter of colourless corpuscles. The diameter of the latter he had already found to vary from 1/2800 to 1/3200 of an inch, slightly above that of the red corpuscles. The 'molecules' were present within colourless corpuscles, free in the surrounding fluid, in the interior of pus corpuscles and free within the mucus itself. In the blood of another patient, a forty-year-old man with acute rheumatism, he found similar granules. After adding dilute acetic acid to a drop of this patient's blood and examining it under the microscope between two slips of glass he saw that the red corpuscles quickly lost their colour and became almost invisible, while the white corpuscles and their contained granules became prominent. Addison concluded that the colourless blood corpuscles were identical with the

pus corpuscles described by Gulliver,[13] since both contained similar molecules or granules and reacted alike to dilute acetic acid. But, wrote Addison, 'as the term pus denotes an abnormal and *extra*vascular product, it seems inappropriate to apply the term pus corpuscle to an *intra*vascular corpuscle circulating in the blood, and the existence of which, *within certain limits, is perfectly normal*'. He then reported an interesting clinical finding. In one of his patients, a young woman with a severely inflamed finger and hand, he 'pricked the skin over the knuckle, where it was extremely tense and red, and placed a drop of blood diluted with weak acid under the microscope. There were hundreds of large colourless corpuscles, with well-marked granules in their interior.' As a control observation he pricked the back of the hand of a woman suffering from a slight cold but otherwise well and found only a few such corpuscles. The colourless corpuscle, Addison thought, was equivalent to the 'cytoblast' of Valentin or the 'nucleus' of Brown, and it was apparently brought into existence by the aggregation of minute molecules or granules present in the 'nutritive fluids of vegetables and animals'.[14] In this same paper Addison returns to his experimental observations on the frog to say that the lymph globules seen in the vessels of the foot web also have molecules or granules within, and are 'strictly analogous' to the colourless corpuscles of human blood. And this not only in respect to their structure, but also by reason of their invariable accumulation in large numbers in 'vessels in which inflammatory action has been excited'. The molecules or granules in question have been repeatedly described, says Addison, in the epithelium of mucous membranes, in ciliated cylindrical bronchial epithelium, and elsewhere in both plants and animals, but he is unaware that they have ever been noticed in human blood.

Up to this time we have seen Addison attempt to explain the genesis of the inflammatory crust or buffy coat of the blood, call attention to the presence of colourless corpuscles accumulated in the capillaries of the frog's foot web when inflamed, and note the greatly increased number of colour-

less corpuscles in blood pricked from the inflamed finger of a young woman. He has in addition identified pus corpuscles in the tissues with circulating colourless corpuscles in the blood. This identification would seem to require the assumption of their passage from the blood into the tissues. No doubt this was Addison's opinion, although he had not expressed it overtly, much less described the mode of passage explicitly. We have seen him shift his opinions slightly, perhaps, since the communication of 14 March 1841 in which he apparently bypassed the question of whether the white blood globules (now referred to always as corpuscles) leave the vascular channels, after stating that the red globules did not. The implication that the white blood corpuscles leave the bloodstream is now clear. But as to what they do (other than become pus corpuscles) or what this may mean he has expressed no opinion. That is, until his reply to Jones. Then, as if goaded, he summarizes in a postscript some findings and hypotheses that are to be published fully in the *Transactions of the Provincial Medical and Surgical Association* in the following year. The colourless corpuscles, he says, are highly organized vesicles or cells formed from the central portion of the red corpuscles and 'they combine with, or adhere to, the tissues through which the minute currents of the blood circulate, and become cells, performing different functions, and assuming different forms, in various parts of the body, in accordance with the primitive law regulating the development of the organism'.

Bibliography and Notes

1. William Addison, 'Colourless globules in the buffy coat of the blood', *Lond. med. Gaz.*, N.S., 1840–41, i, 477–79.
2. *Cyclopaedia of Practical Medicine*, ed. by John Forbes, Alexander Tweedy and John Conolly, London, 1833. Cf. pp. 721–23, where it is pointed out that when the physician engaged in therapeutic blood-letting makes an unusually small opening in a vein, so that the blood issues forth very slowly, clotting may take place before the buffy coat has time to form. After free flow has been established the buffy coat will appear. Sometimes the first cup of blood will display a well formed buffy coat, the

second a scanty coat and the third none at all. The writer attributes this phenomenon to the 'immediate diminution of inflammatory symptoms' with which 'bleeding is frequently attended'.

3. (a) To prepare a Coddington lens a deep equatorial groove is ground in a glass sphere and filled with opaque matter, thus limiting the aperture and, in consequence, reducing aberration. Some so-called Coddington lenses were made by cementing together two plano-convex lenses with a stop interposed (William B. Carpenter, *The Microscope and its Revelations*, Philadelphia, 1865, pp. 80, 81).

   (b) Benjamin Babington also found that the 'opalescent and viscid fluid' forming on the top of buffy blood could be withdrawn from the underlying red cells before coagulation occurred. Afterwards it separated into clot and serum. Babington did not comment on the white globules, however ('Some considerations with respect to the blood', *Med. Chir. Trans.*, 1830, **16**, 293, 319.)

4. Addison, 'Colourless globules', loc. cit., p. 479. Addison's description of the buffy coat here may advantageously be compared with that by Henry Ancell, made at about the same time. Ancell states that the 'upper part of the coagulum, *through* which the red corpuscles have time to subside, furnishes the buffy coat; while the portion *into* which the red corpuscles descend, furnishes the coloured clot' ('Course of lectures on the physiology and pathology of the blood, etc.', Lect. XIX, *Lancet*, 1840, **ii**, 661–71; cf. p. 669). The white globules or corpuscles play no part in Ancell's account of the formation of the buffy coat.

5. Addison cites here Johannes Müller's 'Physiology', with no further bibliographic details. He could have used Baly's translation of vol. I (*Elements of Physiology by J. Mueller, M.D., Professor of Anatomy and Physiology in the University of Berlin*, etc., trans. by William Baly, vol. I, London, 1838).

6. Addison, 'Colourless globules' (cont.), *Lond. med. Gaz.*, op. cit., pp. 689–93.

7. Ibid., p. 691.

8. William Addison, 'On the colourless globules and other elements of the blood', *Lond. med. Gaz.*, N.S., 1840–41, **ii**, 13–15.

9. Theodor Schwann, *Mikroskopische Untersuchungen ueber die Uebereinstimmung in der Struktur und dem Wachstum der Thiere und Pflanzen*, Berlin, 1839.

10. Thomas Wharton Jones, 'Observations on some points in the anatomy, physiology, and pathology of the blood', *Brit. for. med. Rev.*, 1842, **14**, 585–600.

11. William Addison, 'Mr. Addison's remarks on Mr. T. Wharton Jones' observations on the blood', *Lond. med. Gaz.*, N.S., 1842–43, **i**, 180.

12. William Addison, 'On the colourless corpuscles, and on the molecules and cytoblasts in the blood', *Lond. med. Gaz.*, N.S., 1841–42, **ii**, 144–48. Jones was not the only one to understand Addison in this way. Martin

Barry did so as well ('On the corpuscles of the blood', *Phil. Trans. R. Soc. Lond.*, 1840, pt. I, p. 114).

13. (a) Addison did not cite a specific article by Gulliver at this point. Henry Ancell (op. cit., Lect. XX, pp. 739–49) mentioned in 1840 that Gulliver had detected pus globules in the blood of patients with hectic and inflammatory fevers and in almost every instance of suppuration. Ancell himself, also in 1840, states that he and Lane found large white corpuscles, resembling those seen in pus and mucus, to be present in normal blood: 'Although few in number, they are constant in the blood of animals, including man.' He notes that Magendie, among others, had made the same finding (op. cit., Lect. XXI, *Lancet*, **ii**, 772–81; cf. p. 777).

(b) The use of acetic acid in this way had been introduced by Ludwig Gueterbock several years earlier, according to Jacob Henle ('Ueber Schleim-und Eiterbildung', *Hufeland's neues Journal der practischen Arzneikunde*, Bd III, V *Stueck*, pp. 3–62, May 1838).

(c) On 'molecules' see note 14(c).

14. (a) The claim that Addison was the first to comment on an increased number of white cells in the blood in association with inflammatory processes rests on observations of this kind. But Ancell had already noted 'several instances of suppuration in which the white globules of the blood, were much more numerous than those described, as occurring constantly in health; and they had the same form, colour, magnitude, and appearance, as the white globules usually met with in the blood' (op. cit., Lect. XXI, p. 777). George Gulliver pointed out that there were slight differences visible between pus corpuscles and white blood corpuscles. He found that the 'pus-like globules found in the blood of patients affected with severe inflammatory and suppurative disease' were as a rule 'larger, more irregular in size and shape, and much more numerous' than the pale globules seen in the blood of healthy persons. In a fatal case of inflammation and suppuration of the leg Gulliver found that the blood contained about half as many 'pus-like globules' as 'red discs' (*London and Edinburgh Philosophical Magazine*, September 1842; abstracted in *Brit. for. med.-chir. Rev.*, 1843, **15**, 234). Gulliver's case may have been one of leukaemia (cf. Ch. II.5 for more on pyaemia, leucocytosis and leukaemia).

(b) Gulliver's elaborately annotated edition of William Hewson's *Experimental Inquiries* (1772–74) is an invaluable source of information regarding the haematology of the time (*The Works of William Hewson, F.R.S. Edited With an Introduction and Notes by George Gulliver, F.R.S.*, London, 1846). In Part III, dealing with the lymph glands, thymus and spleen (edited in 1777, after the death of Hewson, by Magnus Falconer), Hewson makes the following highly interesting statement: 'Secondly, we have proved that vast numbers of central particles made by the thymus and lymphatic glands, are poured into the blood-vessels

through the thoracic duct, and if we examine the blood attentively we see them floating in it. Nature surely would not make so infinitely many particles to answer to no purpose! What then becomes of these particles after they are mixed with the circulating blood; are they immediately destroyed? No. They are, we believe, carried with the blood to the spleen . . . the spleen has the power of depositing them in the cells [N.B. 'cells' here = 'compartments'] of that gland already described; where the arteries which are spread out in the form of network upon the sides of the cells secrete from the blood the vesicular portion [i.e. the corpuscles], and that when thus perfectly made, the lymphatic vessels which originate from the cells absorb them, and convey them thence into the thoracic duct, and so into the blood-vessels' (op. cit., pp. 282–83). Aside from the interest that Hewson's concept of the circulation of lymph corpuscles will have to those familiar with recent developments in immunology, the passage shows that he recognized the white corpuscle as a normal inhabitant of the blood. Gulliver notes here that this 'passage is so clear, as completely to set aside the claim of late years made by M. Mandl and others to the discovery of the pale globules of the blood'. In this connexion Gulliver mentions also Jean Baptiste Senac's alleged description, in 1749, of the pale globules, pointing out that Senac seems 'to have regarded them as belonging to the chyle' (ibid., p. 282). Senac's observations may be found, according to Gulliver, in the *Traité du coeur*, 1749, vol. 2, pp. 91, 661; they will not be discussed here. Those of Louis Mandl are worth noting, however. Mandl states that the 'globules of pus and mucus are the same as the fibrinous white globules of the blood'. Dissolved fibrin in the blood passes through vascular walls, 'in accord with the laws of endosmosis and exosmosis', and by virtue of a coagulatory process globules are formed anew as pus and mucous corpuscles (*Mémoires sur les parties microscopiques du pus et du mucus*, Paris, 1839). This is in line with blastema theory (cf. Ch. I.2).

(c) With reference to Valentin see Ch. I.2, note 11. Robert Brown was, according to John R. Baker, the first observer to recognize (in 1833) that the 'nucleus' or 'areola' of the 'cell' was regularly present; he also coined the term nucleus for this part of the cell ('The Cell-Theory: A Restatement, History and Critique, Part II', *Quart. J. microsc. Sci.*, 1949, 90/1, 101; for comments on the 'nucleus' before Brown see Baker, loc. cit., pp. 97–101) Brown's somewhat earlier observations on the movement of 'molecules' suspended in fluid media (now termed Brownian movement) are pertinent here, since Addison saw and made far-reaching inferences from these movements. Brown's observations were published in 1828 ('A Brief Account of Microscopical Observations made in the Months of June, July, and August, 1827, on the Particles Contained in the Pollen of Plants; and on the General Existence of Active Molecules in Organic and Inorganic Bodies', *Edinb. New philos. J.*, 1828, 5, 358–71). Using a simple microscope consisting of a double

convex lens with a focal distance of 1/52 inch (supplied by 'Mr. Bancks, optician in the Strand') Brown saw 'rapid oscillatory motion' of 'smaller particles, or Molecules, as I shall term them' in a wide variety of finely particulate organic and inorganic matter suspended in fluid media. With a micrometer he determined the particles to be between 1/15,000 and 1/20,000 of an inch in diameter. Brown writes that some of the smaller particles displaying these movements are the 'supposed constituent or elementary molecules of organic bodies, first so considered by Buffon and Needham, then by Wrisberg with greater precision, soon after and still more particularly by Mueller, and very recently, by Dr. Milne Edwards, who has revived the doctrine and supported it with much interesting detail' (op. cit., p. 363).

I.2 Cells, Fibres and Blastema

In the preceding section we have heard of 'globules', 'fibres', 'corpuscles', 'cells' and 'blastema'. Some will perhaps wonder about the relationship between these terms, while the biologically more sophisticated reader will understand 'globule' and 'corpuscle' as antiquated terms for 'cell'; as for 'blastema', he will recognize that a change of meaning must have taken place, for the term now signifies an as yet unformed mass of cells where it once meant an amorphous or finely granular mass capable of forming fibres and cells. Before continuing with our examination of Addison's published work in relation to that of his contemporaries it will be helpful to consider briefly the more important of the concepts associated with the above terms, and in addition to give some thought to the problem of how objects in the microscopical world are 'seen', i.e. recognized or discriminated as such. We need to place ourselves, insofar as this is possible, in the position of a microscopist in the early eighteen forties.

The human activity of 'seeing' cannot properly be understood as the mere camera-like registration of visible objects external to ourselves waiting, so to speak, to be photographed by the eye. The extent to which 'seeing', 'seeing as', 'discriminating' and 'interpreting' are combined in an

apparently single act has attracted much attention in recent years from philosophers of science and psychologists, but historians of scientific discovery have so far failed to use the results of these investigations when they attempt to answer such questions as, Who first saw the cell?, white cells?, diapedesis?, and so on.[1]

Woodger pointed out some time ago in this connexion that seeing is always interpreting. A beginner looking through a microscope today at a stained section of plant or animal tissue will see a confusion of colours and patterns. The objects—really conceptual objects—so clearly seen by his instructor are simply not there for him and it is at the cost of much time and effort on the part of both that he learns to discriminate, i.e. to ignore what does not signify for what does, and so to see what is properly there. We call this activity seeing but it is clearly a first step in interpreting. Like the man blind almost from birth who has been restored to sight and is at first incapable of discriminating simple objects hitherto familiar to him by touch from their visual background, or even of telling a man from a cow just by looking, so the student first introduced into the microscopical world cannot 'see' the essential difference between, say, a section of liver, spleen or kidney. Yet he is making use of tissue sections fixed to immobility and stained in different colours to bring out the desired discriminations, while the microscopists of the eighteen forties examined fresh, unstained tissues, often in living animals, using moreover the relatively imperfect microscopes then available.[2]

Still another difficulty arises in connexion with an attempt to place ourselves in the position of and to understand a scientific worker of an earlier time. This one is of linguistic character. When a word, say 'cell', has come to mean whatever it does mean at any given time in the course of biological thought there arises a strong tendency on our part to suppose that an earlier worker who used this word must have meant approximately the same thing. The tendency is so strong that even if we are aware that changes take place in the use of words we may yet deceive ourselves.[3]

This history of the cell concept furnishes an illuminating instance. Historians of science almost invariably place Robert Hooke (1635–1703) at the beginning of this development in scientific thought, yet a careful reading of the *Micrographia* will show that Hooke's comments on the 'cell' have nothing at all to do with the discernment of the cell as the ultimate structural and functional unit of plant and animal tissues. In the one passage where Hooke discussed this aspect of the matter he expressed the then current belief that animal tissues were built up of 'fibres', in the manner of a woven fabric.[4]

The history of the fibre as the primary unit of structure goes back at least to Aristotle.[5] In the *Historia animalium* he describes two classes of fibres, one of which is found in the solid tissues occupying a position intermediate between 'sinew' (*neuron*) and 'vessel' (*phleps*). The other, interestingly enough, is the 'fibre' found in clotted blood, i.e. our 'fibrin'. In the eighteenth century von Haller said that the fibre was to the physiologist what the line was to the geometer.[6] At the end of that century Reil called the fibre the 'simplest organ', the ultimate component of all tissues. It formed from a fluid matrix by a process of 'animal crystallization'.[7] Most anatomists and physiologists of the time, it is fair to say, would have agreed that such fibres, themselves built up of organic particles, were the basic structural units of both plant and animal tissues. The matrix out of which the fibres were supposed to form later received the name 'blastema' as we have already seen. It is interesting, in the light of Schwann's cell theory, that Reil thought that a 'germ' (Keim) or *nucleus* was needed, around which crystallization took place, presumably by analogy with the crystallization of inorganic solutions around particles introduced into the fluid.[8]

The 'cell' was destined to displace the 'fibre' from its position as primary structural unit. This process took place rather gradually during the second quarter of the nineteenth century. The displacement process culminated in 1839 with the publication of Theodor Schwann's (1810–1882)

book on the cell.[9] An interesting sidelight on the rivalry between cell and fibre in England is cast by some remarks of George Gulliver, the eminent anatomist and haematologist, made in 1842. 'The well-known theory of Dr. Schwann', he wrote, 'ascribes the origin of all tissues to the formation in the first instance of round cells, and the change of these into the various fibres and other textures.' But if this be so how, asks Gulliver, is the 'origin of the fibrils of fibrin to be reconciled with the theory of Dr. Schwann? What is the proof that these fibrils may not be the primordial fibres of many animal textures?' Gulliver's remarks illustrate not only resistance to the cell theory but more importantly, for our purposes, they show the position occupied by the formation of fibres from the fluid blood as paradigmatic for the formation of 'textures', i.e. tissues, generally. Gulliver could find, he wrote, no evidence that the fibrils of fibrin were transformed cells. They formed so quickly during coagulation that 'their production according to Dr. Schwann would seem impossible'. Gulliver rejected also the observations of Barry purporting to show that the fibrin fibrils came from the interior of red cells.[10]

The ideas and findings of Theodor Schwann on cells became available in English for the first time in 1841, in Willis' translation of Wagner's *Lehrbuch der Physiologie*.[11] Schwann and his rival Valentin had both contributed brief notes to this work. Schwann's note states that all organic tissues have 'one common principle of development as their basis, viz. the formation of cells; that is to say, Nature never unites molecules immediately into a fibre, a tube, and so forth, but she always in the first instance forms a round cell, or changes, when it is requisite, cells into various primary tissues'. Schwann's molecules should of course be understood as the molecules of the microscopist. Next we see how easily the cell fitted into the prevailing theory of the blastema: 'There is first a structureless substance present (cytoblastema) which is either contained in pre-existing cells, or exists on the outside of these. Within this, cell-nuclei generally first arise—round or oval, spherical or flat

corpuscles—which usually include one or two small dark points (nuclear corpuscles). Around these cell-nuclei the cells are produced, and in such wise that they at first surround the nuclei closely'.[12]

Schwann's cell theory as stated above makes two independent claims, firstly that cells form from a structureless blastema, now called the cytoblastema, and secondly that all structural components of the body, all tissues and organs, are derived by the transformation and combination of cells. Most of Schwann's book is devoted to a careful demonstration of the second part of his thesis, and we shall see later what bearing his studies of the formation of capillaries had on the question of whether or how the white cells pass through their walls. The precise manner in which cells formed out of the amorphous or finely granular (molecular) cytoblastema was the subject of much controversy down to the eighteen fifties. But this part of the theory was to be discarded by almost everyone, including Schwann himself presumably, within two decades after the publication of his book. Even from the beginning there were some who had never accepted it.[13]

How familiar Addison was with these developments in anatomical and physiological theory we do not know. It is evident that by 1842 he understood something of cell theory, although he mentions only the work of Schleiden (from whom Schwann had drawn inspiration) and Valentin. We shall see in the following section in more detail how Addison came to reject the prevailing view that the white corpuscles seen at sites of inflammation were formed from an exuded blastema. We shall also become acquainted with some of his ideas on the nature of cells.

Bibliography and Notes

1. Cf. M. L. Johnson Abercrombie's *The Anatomy of Judgement*, New York, 1960, especially the second and third chapters dealing with schemata and their role in visual interpretation. N. R. Hanson's *Patterns of Discovery*, Cambridge, 1958, contains much that is pertinent to the above discussion,

although it deals chiefly with problems in the physical sciences from the standpoint of a philosopher of science. One of the tasks we face in attempting to trace sequences of discovery in the sciences is, Hanson writes, that of showing how visual data are moulded by different theories, interpretations or intellectual constructions. See also Joseph Agassi's 'Towards an Historiography of Science', in *History and Theory*, Beiheft 2, 1963. He writes that Bacon's inductive philosophy of science left an imprint on the history of science as well, and describes 'inductive' historians of science as textbook worshippers whose own work consists of the material in an up-to-date textbook arranged in chronological order together with notes on its origin, a few biographical data thrown in. The working formula of the inductivist historian is 'in the year X scientist Y discovered fact (or theory) Z'. The 'comparative' approach, which Agassi favours, avoids being wise after the event and allows us to relive scientific experiences by studying them against the background of contemporary thought.

2. Cf. J. H. Woodger's *Biological Principles. A Critical Study*, London 1929. Woodger observes that the beginning student 'is, as it were, "born again" through the microscope. He is an infant in the microscopical world. He cannot perceive things in that world because he does not possess the requisite thought-objects . . . His teacher, on the other hand, has lived longer in the microscopical world and has developed the requisite thoughts and therefore sees, not a confused blur but sharply defined objects . . . What to the pupil is a confusion in a wider confusion and scarcely if at all discriminated from it, is for him a section of a blood-vessel related in a definite way to other tissues or organs' (pp. 136, 137).
3. John R. Baker pointed out not long ago that some historians had been misled by the phrase *tissu cellulaire* into supposing that users (in the eighteenth and early nineteenth centuries) were referring to 'cells' in the modern sense of the term. Nevertheless he himself fell into this error at one point, in connexion with a reference to 'cells' in a passage by William Hewson, written in the late eighteenth century. Hewson's words were: 'Then if we carefully wipe or wash this fluid from any part of the cut surface of a lymph node, and examine it attentively in the microscope we observe an almost infinite number of small cells, such as have been described. . . .' But the pronoun 'it' refers here to 'cut surface' and not to 'fluid', as Baker supposed, for in the very next paragraph Hewson adds that if the vessels be injected with a coloured fluid and the tissue then examined under the microscope, 'we observe that these cells are extremely vascular'. For Baker's remarks see his paper cited in Ch. I (Pt. 1, pp. 103–5). For Hewson, op. cit., p. 251. See also Hewson's use of the word 'cell' in the passage quoted in Ch. I, note 14(b).
4. (a) A few examples will suffice to show the place usually given to Hooke by historians of science. 'Robert Hooke discovered that plant tissues have a characteristic cellular structure. His *Micrographia* contained

magnified illustrations of cork cells . . .' (*History of Science: The Beginnings of Modern Science*, edited by René Taton and trans. from the French by A. J. Pomerans, New York, 1964, p. 367); *World Who's Who in Science* (op. cit.) credits Hooke with no more than the discovery of 'honeycomb cavities (which he called cells) in thin sections of cork', which is accurate enough, although still carrying a certain degree of confusion between word and concept; Garrison and Morton (op. cit.) say that the *Micrographia* 'includes also the first reference to cells', which is quite misleading and not even true (see Bacon's remarks cited below). Hooke in fact, used the terms 'cell', 'pore', 'little box', 'channel' and 'pipe' sometimes rather indiscriminately in the *Micrographia*. In Obs. XVIII he describes the surface of cork as 'perforated and porous, much like a honeycomb'. The pores, he writes, are 'channels or pipes' through which the juices of the plant are transported. Although Hooke was unable to find a 'passage out from any one of those cavities into another', he refused to believe that none was present. His reason was that 'in several vegetables while green I have discovered these cells or poles [*sic*] filled with juices and by degrees sweating them out'. Hooke's equation of 'cells' and 'poles' (obviously a misprint for 'pores') is very revealing. In Obs. XVI he finds pores in charcoal and adds that all woods have such 'pipes and sluices' through which the nutritive juices flow. In Obs. XVII he discovers pores in petrified wood. In Obs. XV there is a revealing discussion of a mineral conglomerate, called 'Kettering-Stone', made up, says Hooke, of innumerable 'small globules' or 'globular balls'. He adds: 'And so I guess the pores in wood and other vegetables, in bones and other animal substances to be as so many channels. . . .' He even extends his theory of pores to include glass, where the presence of invisibly small pores is supposed to allow for the passage of light. Finally, in Obs. XXII, Hooke compares animal substance to a 'text of filaments', such as he has seen in tanned leather, and to the 'infinite company of small filaments every way contexted and woven together, so as to make a kind of cloth', constituting the substance of mushrooms (*Micrographia*, London, 1665). Hooke's 'cell' (in his sense) was a pore or opening; his 'cell' (in our sense) was, insofar as he had one, a 'fibre', paradoxical as it may seem.

(b) Francis Bacon, before Hooke, used the term 'cell' in this sense. Bacon tells us that we must inquire into the 'position of the Spirit through the corporeal mass, its pores, passages, veins, cells [*cellulae*], and rudiments or first essays of the organic body . . .' (*Novum Organoun. A new Translation by Rev. G. W. Kitchin*, Oxford, 1855, p. 123 (Bk. II/7)). In this passage 'cells' are not 'rudiments', as we might be tempted to suppose (on the assumption that Bacon dipped into the future for his meaning), but one of a variety of open spaces—pores, passages, veins and cells—in the body. Hooke, likewise, equated cells and pores, as we have seen.

5. Cf. Bk. III/6, 515(b) of *The Works of Aristotle*, trans. into English under the editorship of J. A. Smith and W. D. Ross, vol. IV, *Historia Animalium*, by D'Arcy Wentworth Thompson, Oxford, 1910: 'The *ines* (or fibrous connective tissues) are a something intermediate between sinew and vein . . . There is another kind of *ines* or fibre found in the blood . . . If this fibre be left in the blood will coagulate; if it be removed or extracted, the blood is found incapable of coagulation.' Note that the similarity seen by Aristotle between fibres in the tissues and in coagulated blood still appealed to upholders of the blastema theory, such as Gulliver, in the mid-nineteenth century.
6. Albrecht von Haller, *Elementa physiologiae corporis humani*, 8 vols., Lausanne, 1757–66, vol. 1, p. 2.
7. Johann Christian Reil, 'Von der Lebenskraft', *Arch. Physiol.*, 1759; reprinted in Sudhoff's *Klassiker der Medizin*, Leipzig, 1910, cf. pp. 37, 38.
8. Ibid., pp. 42, 43.
9. Schwann, *Mikroskopische Untersuchungen*, op. cit. Cf. L. J. Rather, 'Some relations between eighteenth century fibre theory and nineteenth century cell theory', *Clio Medica*, 1969, 4, 191–202.
10. George Gulliver, 'On the structure of fibrin and of false membranes: origin of fibre', *Lond. Edinb. philos. Mag.*, October 1842, p. 234.
11. Rudolf Wagner, *Elements of Physiology*, trans. by Robert Willis, London, 1841. Gabriel Valentin's contribution occupies pp. 214–21. With reference to Hooke's 'pores' the following remark by Valentin is interesting: 'The cells exhibit metamorphoses, which in point of form are in all respects analogous to those we observe during the formation of wood, and indeed of the pores, in plants' (loc. cit., p. 216). On p. 218 Valentin writes that the 'cells exhibit a very high degree of productive or procreative power. New cells are perpetually arising within them and there surrounding themselves with cells, we have finally cell within cell, like a nest of pill boxes.' For a recent assessment of Valentin's role in cell theory see Erich Hintzsche's 'Zellen und Gewebe in G. Valentins "Histiogenia comparata" von 1835 und 1839', *Berner Beitr. Gesch. Med. Naturwiss.*, Nr. 20, Berne, 1963.
12. Schwann's statement of his cell theory occupies pp. 222–26 of Willis' translation of Wagner.
13. Cf. Ch. III.1 and note 4.

I.3 Addison's First Major Article

(Transactions of the Provincial Medical and Surgical Association 1843).

Up to this time Addison's papers had been no more than short reports of his clinical and experimental findings. He was now ready to turn out a larger paper in which some of the various threads of his corpuscular doctrine would be drawn together. His article in the *Transactions* comes to seventy-four pages and is divided into seven sections: 1. human blood corpuscles; 2. pus corpuscles; 3. the blood corpuscles and lymph globules of the frog; 4. inflammation; 5. cells, vegetables and animal; 6. the aeriferous structure of the lungs; and 7. the mode of formation of tubercles.[1]

He begins with a reference to some recently published work by Martin Barry in which that observer asserts that every tissue arises 'out of corpuscles having the same appearance as the corpuscles of the blood'.[2] Anticipating what he will set forth in detail later Addison now states that he himself has found that all varieties of epithelial cells and pus corpuscles arise from the colourless corpuscles of the blood, and further that the cellular formations met with in tubercular infiltrates and pneumonic hepatization in the lungs have exactly the same origin.[3] Addison has previously referred to 'molecules' and 'granules' interchangeably. He now offers some measurements and a more precise distinction of the two. His microscope, he tells us, has a linear magnification of 250 and 500 diameters. Using the lower power and comparing the size of black spots seen on a white background with the naked eye to those seen in the blood he estimates that the 'molecules' cannot exceed 1/100,000 of an inch. The 'granules' are defined as objects visible as bright points surrounded by dark circles measuring about $\frac{1}{4}$ or $\frac{1}{5}$ the diameter of a red blood corpuscle, that is about 1/11,000 to 1/14,000 of an inch. He admits that precise measurement of objects so small is out of the question.[4]

The human red corpuscle exhibits 'an appearance of two

circles, one within the other', and he supposes that it consists of two elastic vesicles with colouring matter occupying the space between. The central portion of the red corpuscle is occupied by a 'peculiar matter'. Addison is aware that his description does not accord with the usual one given of red corpuscles in human blood.[5]

In addition to the red corpuscles the blood always contains a small number of circular, 'softer' colourless corpuscles, best seen by examining a drop of blood pressed between two slips of glass and placed under the microscope. By carrying out this manoeuvre with 'blood just drawn from an inflamed surface, as a pimple or the base of a boil, they are found abundant; and in the blood taken from the skin of a patient in scarlet fever, or from the spots of any cutaneous disease, they are remarkably numerous and conspicuous'.[6] They are most conveniently obtained from the fluid at the surface of the buffy coat before it coagulates. These colourless corpuscles, says Addison, have been seen by many observers and have been designated lymph globules, pus globules, white blood globules, blood corpuscles of the second form, and exudation corpuscles. With respect to the propriety of the last of these Addison says that in all of his examinations of buffy blood he has never seen fibrin aggregate to form molecules, granules or corpuscles. Instead it always forms delicate fibres or filaments that 'gradually increase in number, intersecting each other in various directions, and at length form a complete network, in the meshes and angles of which the colourless corpuscles and the molecules and granules are entangled and drawn together, forming with variable portions of included serum the entire mass of the buffy coat of the blood'.[7] (Addison's description of the mode of formation of the buffy coat has now become more precise.) The above observation is important, for according to the blastema theory it was precisely in this way that pus corpuscles were formed from exuded fibrinous blastema.[8]

When dilute acetic acid was added to a drop of blood Addison saw that the red corpuscles dissolved, while the granules of the white corpuscles became more prominent.

After a while the white corpuscles burst, setting free a number of granules and molecules. Dilute solutions of ammonia water or *liquor potassae* had the same effect on the white corpuscles.[9] And the same changes could be observed after the use of these fluids on the corpuscles found in abscesses and muco-purulent discharges and in the clear fluid of shingles vesicles and inflammatory oedema. From all of this Addison concluded that 'pus corpuscles of all kinds are altered colourless corpuscles'. No new elementary particles were formed by inflammatory or diseased action, he adds, again rejecting the blastema hypothesis.[10]

What is the origin of the colourless corpuscle in the circulating blood? On this subject Addison presented some novel observations of his own, carried out on frogs' blood. The red corpuscles of the frog are much larger than those of man and the mammals generally.[11] Starting from the assumption that the colourless globules in the blood of the frog were analogous to the colourless corpuscles in human blood, Addison thought that he could observe under the microscope a stripping off of the 'outer vesicles' of the frog red corpuscles after treatment with *liquor potassae*. A body of about the size and shape of a lymph globule or colourless corpuscle was revealed. His experiments, he wrote, 'appear to show that the lymph globule of the frog is the inner vesicle or central portion of the red corpuscle, and its structure is similar to that of the colourless blood corpuscle of man . . . we have strong ground for concluding that the colourless blood and pus corpuscles of man are formed from the central portion of the red corpuscles'.[12]

Addison then gives another description of the circulatory events visible in the frog's foot after the application of a crystal of salt. Up to a point it adds little to his earlier account or to those of others. He describes the initial increase in flow rate and the subsequent slowing and congestion followed here and there by oscillatory or retrograde movements of the stream. After a half an hour or so the 'current of the red corpuscles, in some of the veins, appeared to be confined to the centre of the vessel, and not to touch the

circumference, which was occupied by a great many lymph globules'. On the following morning 'the whole interior of the inflamed vessels appeared to be lined with lymph globules. By gently altering the focus of the microscope they were seen below the red current, and many of them appeared to lie externally to the boundary of the vessels.'[13] Addison included in his presentation a drawing of what he had seen, and referred his readers to some figures in Rudolph Wagner's *Icones Physiologicae* that, in his opinion at least, supported his claims. He also referred to an article by James Paget in the *British and Foreign Medical Review* and adopted one of Paget's descriptive phrases, saying that where the lymph globules were present in large number 'the red current appeared as if passing over a bed of marbles'.[14] The observed phenomena, said Addison, 'corroborate the views of those distinguished physiologists who entertain the opinion that the capillary distribution of the blood is situated in channels of the tissue and not in vessels with a distinct membraneous coat'.[15] The 'walls' bounding the capillaries became more evident in inflamed vessels, but they appeared to consist only of parallel fibrinous fibres that gradually amalgamated with the structure of the tissue. And 'it is among these fibrinous looking fibres that the lymph globules are seen to accumulate'.[15]

The fifth section of Addison's article in the *Transactions* is concerned with the cell, a term now occurring with increasing frequency in his writings. Taking support from some work published by Martin Barry between 1839 and 1842, as well as from his own observations, Addison now states that there can be no doubt but that the formation of new cells in the higher animals is confined to the blood and chyle, that 'the tissue or epithelial cells have not the power of reproducing their kind'. Once the white corpuscles have left the bloodstream they are no longer capable of acting as 'parent cells' (one of Barry's terms). Instead they form pus corpuscles or various tissue cells. Cells are independent functional units, writes Addison, and their chief function in the tissues is the elaboration of secretions.[16] He discusses the

cells of several species of plants, furnishing drawings of what he has seen under the microscope, and mentions that the cells of vegetable structures also appear to be functionally independent from one another. In passing he makes a reference to the 'admirable researches of Schleiden and Schwann' and to those of John Goodsir. It is Goodsir's opinion that 'all the secretions of the animal tissues are formed in the interior of vesicles or cells'.[17] After examining liver cells under the microscope and observing that the application of acetic acid caused them to reveal a content of granules resembling those seen in white corpuscles Addison remarks that it is 'impossible to adduce any direct proof that the granulated vesicles of the liver are formed from colourless blood corpuscles, but the details of their structure render the supposition by no means improbable'. He thought also that he could observe forms transitional between colourless corpuscles, pus corpuscles and pavement epithelial cells in fluid drawn from an inflammatory blister.[18]

Addison's conclusion was, in his own words, that 'all varieties of epithelial cells are formed by colourless blood corpuscles'.[19] And by 'epithelial' he means, of course, not only the cells of pavement epithelium but also those found in such parenchymal organs as the liver. In support of the conclusion he brought forward the same observation that we have seen Gulliver adduce in connexion with his query of Schwann's doctrine: Addison had never seen the fibrin of the blood form granules, corpuscles or globules of any kind while undergoing coagulation. Instead the granules were present within cells, and under special circumstances might be discharged from them.[20] The granules in the 'parent cells', i.e. the colourless cells circulating in the blood, were reproductive units capable of becoming young cells after their discharge, those in the 'tissue cells' had lost their reproductive power. Instead they ministered to the secretory and nutritive needs of the organism, assuming different forms and functions as required.[21] Addison observed the resemblance of certain of the pus corpuscles to the minute living organisms known in his time as 'polygastric animal-

cules'. He found that *liquor potassae* caused these creatures also to burst and discharge granules.[22] Likewise with pollen grains, the spores of fungi and certain cells in the reproductive organs of earthworms, all of which he studied under the microscope. The granules are reproductive organs or 'germs', he claims.[23] As far as the higher organisms were concerned there were 'two very distinct epochs in the career of cells, during the former of which they circulate independently in the blood, and during the latter, are fixed to and form part of the tissue'.[24] The developmental changes undergone by cells after they had left the blood might follow a normal or an abnormal course. A local accumulation of cells under normal conditions meant no more than increased nutritional function. It constituted a state of 'vital turgescence' (Barry's phrase). But if the cells accumulated under abnormal circumstances a state of 'inflammatory turgescence' was present, and the function of an organ so involved might be damaged or destroyed. The excess cells arrested in their further development became pus corpuscles or gave rise to specific forms of disease.[25]

What are some of the specific forms of disease to which Addison refers here? He answers the question in part himself in the closing section of the paper. One is the disease known to the pathological anatomists of his time as 'tubercle' of the lungs, and Addison moves to this topic after a brief digression on normal pulmonary anatomy. He describes the pulmonary 'air cells' (alveoli in modern terms) as enclosures formed by a membrane continuous with that lining the interior of the bronchi. On the air cell membrane are 'numerous granulated vesicles or cells . . . which appear to constitute the normal form of epithelium'. Capillary blood-vessels ramify between the membraneous layers of adjacent air cells. Addison's observations reveal that when flow through these channels is slowed as a result of inflammatory turgescence some of the 'red corpuscles may become pus corpuscles while stationary in the inflamed vessels'.[26] And this, of course, by the stripping-off process referred to previously.

Using both a Coddington lens and a compound microscope Addison examined tuberculous matter taken from the lungs of several patients who had died from the disease. He found numerous corpuscles, some very large and filled with granules, others highly irregular in size and shape. In addition there were molecules, granules and ciliated cells 'in all stages of growth'. Extending his observations to the lungs of two patients who had died with pneumonia in the stage of 'hepatization', Addison found the air cells here too filled with matter similar to that seen in tubercle, with the addition in one instance of numerous red cells. Furthermore, if croton oil were rubbed on the skin and the matter discharged from points subsequently appearing on the surface examined, again 'objects in all respects similar to those which compose a tubercle will be seen, viz., various kinds of pus corpuscles, large granulated corpuscles . . . and an abundance of molecules or granules'. Tubercles of the lung were therefore composed of objects originating from blood corpuscles that had been arrested in their passage through the lungs. The difference between a tuberculous and an inflammatory process in the lung lay in the character of the cells so arrested. If only the colourless cells are arrested (and subsequently pass out into the lung tissue) the 'morbid actions which ensue are strictly those of an abnormal nutrition . . . but if it extend so far as to interfere with the free circulation of the red corpuscles we then have all the phenomena of inflammation'.[27]

We have now completed our survey of Addison's article in the *Transactions*. In it the main features of his concept of nutrition and inflammation have been presented, although not fully developed. Contrary to the ruling physiological and pathological doctrine of his time he does not believe that the processes of nutrition and inflammation involve the exudation of a proteinaceous formative substance (blastema, plasma) through the continuous membranes forming the walls of the capillaries into the tissues, there to be transformed under normal conditions into their fibrous or cellular components, under abnormal conditions into aggregates of

pus and tubercle. He claims to have demonstrated instead that (a) there are no continuous membrane-like walls lining capillary channels; they are formed of fibres blending in with those of the tissues, and the capillaries are mere channels in the tissue parenchyma, (b) the white corpuscles pass out of these channels and under normal circumstances develop into secretory 'epithelial' cells of all kinds constituting the essential working parts of the tissues, while under abnormal circumstances they become the corpuscles seen in pus and tubercle. We shall enquire later into the historical background of this so-called corpuscular theory of nutrition and inflammation somewhat more thoroughly. For the moment it will suffice to say that in 1842 Robert Willis called attention to the fact that Martin Barry's ideas (on which Addison's rested in part) amounted to a revival of the old corpuscular theory.[28] Addison, unlike Barry, held that the white corpuscles and the white corpuscles alone passed out of the tissues under normal circumstances; the red corpuscles did not take part in normal tissue growth and maintenance but appeared only in connexion with certain forms of severe inflammation, as in hepatization of the lung in pneumonia. Further developments of Addison's corpuscular theory appeared in his monograph of 1844 and an examination of the critical reception accorded his ideas will be deferred until its contents have been summarized for the reader. But before doing so it will be useful to present something of the current state of knowledge regarding the microcirculatory system in Addison's time.

Bibliography and Notes

1. William Addison, 'Experimental and practical researches on the structure and function of blood corpuscles; on inflammation; and on the origin and nature of tubercles in the lungs', *Trans. prov. med. surg. Ass.*, 1843, **11**, 233–306.
2. Ibid., p. 234.
3. Ibid.
4. Ibid., pp. 234–35.
5. Ibid., p. 237.

6. Ibid., pp. 238–40.
7. Ibid., p. 241.
8. Cf. Julius Vogel on inflammation in Rudolph Wagner's *Handwoerterbuch der Physiologie mit Ruecksicht auf physiologische Pathologie*, Braunschweig, 1842, vol. 1, pp. 352–55. He states that the blastema composing inflammatory exudates carries its own developmental potentialities but is dependent also on the local supply of water, oxygen, etc. The local persistence of a cause of inflammation favours the development of pus corpuscles from the blastema. T. Wharton Jones in his 'Report on the changes in the blood in inflammation and on the nature of the healing process' (*Brit. for. med. Rev.*, 1844, **18**, 255–80) seems to be in agreement with Henle and Vogel (whose conclusions he reports) that pus corpuscles originate from a blastema exuded from vessels at sites of inflammation.
9. Addison, *Transactions*, op. cit., pp. 242–46.
10. Ibid., pp. 247–53. In support of his statement that no new elementary particles are formed by inflammatory or diseased action Addison cites Johannes Müller's 'On the Nature and Structural Characteristics of Cancer' (1840), the English translation of *Ueber die feinern Bau und die Formen der krankhaften Geschwuelste* (Berlin, 1838). Addison seems unaware that Müller was one of the chief proponents of the blastema hypothesis. The essay on tumours makes use of the new theory of Schwann, including the notion of the cytoblastema. Schwann's discoveries regarding healthy tissue are the best foundation for studies of the developmental history of cellular tumours, writes Müller (op. cit., p. 7).
11. Johannes Müller, *Handbuch der Physiologie des Menschen* (Koblenz, 1833). Taking no account of the colourless corpuscles at this time, Müller filtered out the large red corpuscles of frogs' blood and showed that the clear fluid obtained underwent normal clotting. The usual view, according to Müller, was that the clot was formed by the aggregation of blood corpuscles, and that the cores or 'nuclei' of the red corpuscles were composed of fibrin (op. cit., p. 106).
12. Addison, *Transactions*, op. cit., pp. 253–56.
13. Ibid., p. 257.
14. Ibid., p. 258. For James Paget's article, 'Report on the results obtained by the use of the microscope in the study of human anatomy and physiology' see Ch. II.1.
15. Ibid., pp. 259–60. Addison cites Müller in a footnote, presumably as one of the 'distinguished physiologists', but Müller had by this time changed his mind. Rudolph Wagner, Addison says, claimed that the capillaries were bounded by distinct walls but failed to explain their nature. On the question of capillary walls see Ch. II.1.
16. Ibid., pp. 261–62.
17. Ibid., pp. 265–66.
18. Ibid., pp. 260–70.

19. Ibid., p. 271.
20. Ibid.
21. Ibid., pp. 272–73.
22. Ibid., p. 273. It is plain that Addison did not see amoeboid or other movements on part of the pus corpuscles, for he says of the similarity between them and the polygastric animalcules that it 'would have been difficult to distinguish one from the other, had it not been for the voluntary and very active movements of the animalcules'. Nor did he ever describe movements of the white blood corpuscles. But see II/2, note 13 (b).
23. Ibid., pp. 273–76.
24. Ibid., p. 278.
25. Ibid., pp. 278–79.
26. Ibid., pp. 283–86.
27. Ibid., pp. 287–98. In these pages Addison also makes the statement that 'lepra' of the skin and tubercle in the lung are similar, since the 'essential character of both diseases consists in an accumulation of abnormal or unhealthy epithelial cells derived from vessels in a state of abnormal turgescence. . . .' As the modern histologist recognizes the identical character of the epithelioid granulomas seen in certain forms of leprosy and tuberculosis we might be tempted to credit Addison with another 'first' were we not aware that his description of the tubercle falls far short of being a description of an epithelioid granuloma. While there was disagreement as to whether the formed elements—cells, fibres, etc.—rather than the caseous matter in the tubercle were the essential constituents, it was generally held that the lesion itself represented the result of an outpouring of substance from the blood. Gabriel Andral, in 1829, wrote that 'in the current state of science, the tubercle ought to be considered as the result of a modification or perversion of secretion, preceded or accompanied by active congestion of the blood' (*Précis d'Anatomie pathologique*, Paris, 1829, vol. 1, p. 438). Most investigators of the forties thought that local factors were chiefly determinative of the peculiarities of the lesion. Carl Rokitansky offered a short-lived alternative view. The primary abnormality was in the character of the circulating blastema. In the tuberculous crasis or mixture of the blood 'tuberculous fibrin' made its appearance. Under these circumstances, again given the proper local determining factors, the abnormal blastema—or rather the abnormal fibrinous components of the circulating blastema—exuded from the blood vessels and was deposited locally (*Handbuch der allgemeinen Pathologie*, Vienna, 1846, pp. 549–52).
28. Robert Willis, *Elements of Physiology by Rudolph Wagner*, trans. with additions by Robert Willis, M.D., London, 1841, pp. 447–48.

I.4 The Microcirculation

Current Knowledge in the Second Quarter of the Nineteenth Century.

In order both to counteract any excessive estimate that the reader may have formed regarding the originality of Addison's experimental studies of the events taking place in small blood-vessels following injury or irritation and to indicate the level of current knowledge on this topic at the time when he began his work, a brief historical excursus is necessary.

The capillaries, meaning by this the network of tiny channels connecting the arterial terminations and the venous beginnings, visible only under the microscope, became an object of investigation with the work of Marcello Malpighi in 1661. It had been the opinion of William Harvey, before him, that blood percolated through the tissues somewhat as water permeated the earth.[1] In 1640 Harvey reported some experiments that convinced him of the absence of any 'capillary' vessels binding together the arteries and veins. Harvey made no use of a magnifier and apparently did not foresee that this might be necessary to prove his point.[2] But in 1661 Marcello Malpighi saw, with the aid of a simple microscope, the circulation 'plainly disclosed' in the mesentery of the living frog. He at first assumed, following Harvey, that the blood passed from the arteries to the veins through the interstices of the tissues, but later he examined the dried lung of a frog and described a branching network of small vessels connecting the two sets of larger vessels. These vessels, unlike those Harvey was searching for, were visible only under the microscope.[3]

The number of studies devoted to these vessels was not great during the succeeding century, nor was the ubiquity of their presence in all tissues of men and animals universally accepted. In the eighteenth century Hermann Boerhaave developed a theory of the inflammatory process based on his belief that the vascular system was in essence a network of

branching *conical* tubules of decreasing diameter, the smallest of these being so tiny as not to allow the passage of single red blood globules. Inflammation resulted from an *error loci*, an impaction of the globules in channels too narrow for their passage.[4] In the latter part of the eighteenth century Albrecht von Haller in Germany and Lazzaro Spallanzani in Italy described some features of the microcirculation visible in the living animal, in particular the back and forth movement of the column of blood apparent in small vessels under the microscope following traumatic or chemical injury and thereafter referred to as oscillation.[5]

The nineteenth century opened with the first signs of the flood of new observations on the movement of blood in the smallest vascular channels to be made during the following decades. The favoured, although by no means exclusive, object of experimental study was the foot web of the living frog, and the initial work was done on the British Isles by three men, Wilson Philip, John Thomson and Charles Hastings. Their monographs on the subject were quickly translated into German and French and became the stimulus for further work along this line on the continent.[6] The German investigator Ernst Burdach wrote in 1825 that these three men had, almost alone, first subjected the vascular changes of inflammation to microscopic study.[7] Wilson Philip (1770–1851), a Scot who took his degree at Edinburgh, discussed and rejected the four then current accounts of the vascular changes of inflammation—the *error loci* of Boerhaave and his school, the vascular spasm of Hoffmann and Cullen, the 'morbid lentor of blood clogging the minute vessels' and, lastly, the 'morbidly increased action of the vessels of the inflamed part' (the favourite of English physicians, he says)—in favour of his own observation that the capillaries of the inflamed, i.e. red and swollen, frog foot web were distended and the flow of blood retarded. John Thomson (1765–1846), on the basis of similar studies, claimed that the velocity of the blood in an inflamed zone increased rather than decreased, hence he rejected Wilson Philip's capillary 'debility' as the true cause of the events.

Charles Hastings (1794–1866) then attempted to resolve their differences. His description of the vascular changes visible in the frog foot after mechanical and chemical stimulation is on the whole excellent. Hastings concluded that a temporary stage of capillary vascular excitement with increased rate of flow was followed by 'debility' of the same vessels, characterized by dilatation and slowing of the bloodstream.

Many investigators in Germany had become interested in the study of the microcirculation by the eighteen twenties, and the topic is frequent in doctoral dissertations of the time. At least some of the investigators were using microscopes corrected against spherical aberration. One of the best of these dissertations is by Ernst Burdach, who expressed some doubts on the validity of transferring conclusions drawn from the study of cold-blooded animals to warm-blooded. His procedure was to make a small incision in the abdominal wall of a rabbit, withdraw part of the gut and attached mesenteric membrane and place it on the stage of the microscope. Almost immediately after moistening the membrane with sodium chloride he saw the flow of blood in the capillary channels accelerate sharply. After about fifteen minutes the membrane appeared red and swollen to the naked eye. At this time the 'globules' had become preponderant over the fluid in the capillaries and so many of them were adherent to the capillary walls that the latter had become opaque.[8]

An excellent review of the subject by Karl F. Koch appeared in 1832. He had begun his own work on the capillary vasculature in inflammation while a medical student and in 1825 had submitted a dissertation on the topic for his medical degree. The review is especially valuable for its extensive quotations from the work of his predecessors and summary of points of agreement and disagreement. The most important are as follows: (1) the effect of mild irritants on the small blood vessels is an acceleration of the flow of blood and a decrease in capillary calibre in the affected zone (Spallanzani, Thomson, Wilson Philip, Hastings, Burdach, Kaltenbrunner, Oesterreicher, Wedemeyer, Baumgaertner

and Koch); (2) with long-continued or more intensive action of irritants the flow becomes retarded, the vessels dilate and the globules within appear more closely packed (von Haller, Spallanzani, Hastings, Burdach, Kaltenbrunner, Oesterreicher, Baumgaertner and Koch); (3) a back and forth, oscillatory movement of the globules, hitherto apparent only in larger vessels in the neighbourhood of arteries, becomes visible in the capillary vessels (Leeuwenhoek, von Haller, Spallanzani, Kaltenbrunner, Oesterreicher, Baumgaertner and Koch); (4) the oscillation of globules within the capillaries is synchronous with the pulse beat according to Leeuwenhoek, von Haller, Wedemeyer and Baumgaertner; according to Spallanzani, Oesterreicher and Koch it is not; (5) the corpuscles become less opaque as they dissolve in the serum, and they lend it a reddish, translucent tint (von Haller, Hastings, Kaltenbrunner, Wedemeyer, Baumgaertner and Koch); (6) in the centre of the irritated zone the capillary flow comes to a standstill; beyond this region the changes described under (3), (2) and (1) are visible in that order as distance from the centre increases (von Haller, Spallanzani, Burdach and Koch); (7) if the tissue is allowed to return to normal the changes take place in reverse order (von Haller, Hastings, Kaltenbrunner, Burdach, Baumgaertner and Koch); (8) the stronger the irritant the more rapidly the stasis, accumulation of globules and dilatation of capillaries occur; (9) when the affection is both intense and extensive small arteries and veins participate in the changes (Thomson, Hastings, Kaltenbrunner, Wedemeyer and Koch).[9]

It will be noted that Koch did not include Burdach's observation of the clustering of corpuscles on the margins of irritated capillaries among the points of agreement and disagreement. It would be incorrect to conclude that Burdach was the only one to have seen this phenomenon. The observation that corpuscles sometimes moved slowly along the walls of the smaller blood-vessels and occasionally became adherent had been made before, but no particular importance was attributed to it. The majority of investigators at this

time, Koch and Burdach included, were unable to discriminate clearly at all times between red and white corpuscles in the circulating blood. Given the microscopes at their disposal and their use of living, unstained tissues, this is quite understandable. The so-called red corpuscle is at best a light yellow when seen under these conditions. Furthermore the white corpuscles or 'lymph' corpuscles were at first far more familiar as denizens of the lymph stream than of the blood. Some investigators held that the thinly scattered white globules or corpuscles in the circulating blood (about 1 for every 500 red corpuscles) were derived from red corpuscles by the loss of an outer sheath of colouring matter, others that the 'lymph' corpuscles entered the bloodstream via the lymphatic duct.

The observation that certain of the corpuscles moved slowly along the walls of small vascular channels while the main stream hurried down the central axis of the blood-vessel began to attract more attention later in the eighteen-thirties. In 1836 Jean Poiseuille found that the velocity of the blood corpuscles decreased in direct proportion to their nearness to the vascular wall. Immediately adjacent to the walls of small vessels there was, he said, a transparent and almost corpuscle-free zone that had already been seen by von Haller, Spallanzani and Blainville. The few corpuscles that appeared from time to time in this zone moved along slowly, bumping against the wall and occasionally coming to a complete halt. Poiseuille concluded that the inner layer of the small blood-vessels of reptiles, fish, birds and mammals was covered by a resting layer of serum. When a globule moved from the axial stream to the periphery it gradually slowed down and came to a full stop.[10]

In Poiseuille's paper no distinction was drawn between the red and white globules or corpuscles in the blood. A year later, stimulated by the work of Poiseuille, Ernst Weber of Leipzig carried out some observations of his own on axial flow in small blood-vessels. He came to a different conclusion, based in part on his discrimination of the two kinds of corpuscles. He was aware that lymph-vessels had been

shown (by means of injection experiments) to be present on occasion surrounding blood-vessels somewhat larger than those of capillary diameter. Poiseuille, he said, had failed to observe that the corpuscles moving slowly along the walls in the nearly corpuscle-free zone of small blood-vessels were quite unlike the ordinary red blood corpuscles in appearance. The true explanation of the phenomenon in question was that small blood-vessels, like larger ones, were surrounded by a lymphatic vascular sheath. Thus the two kinds of corpuscles were in reality separated by a transparent, invisible wall.[11] In the same year F. M. Ascherson very tactfully corrected Weber's observation and pointed out why his explanation was untenable. Firstly, the lymph corpuscles could be observed to move always in the same direction as the red corpuscles. Secondly, and more convincingly, the red corpuscles could be seen on occasion to bump up against and dislodge the 'sticky' white corpuscles from the vascular walls.[12] Shortly afterwards Weber expressed his agreement with Ascherson. At the same time he noted that the lymph corpuscles in the blood accumulated at points where there was evident retardation of the blood flow.[13] This work was reviewed and to some extent amplified with his own observations by Wharton Jones in 1842 in an article referred to above (Ch. I/4, Note 10). Wharton Jones gives a very accurate depiction of the events observable in the frog foot web under the microscope. The colourless corpuscles may be seen accumulated at the inner surfaces of the walls of small vessels, 'along which they move very slowly in comparison of the red corpuscles, which occupy the axis of the current'. The white corpuscles 'roll along like round pebbles at the bottom of a stream . . . when the current of blood is slow, a number of corpuscles is observed to be stationary, giving the vessel an appearance as if it were lined with an epithelium of globular corpuscles; a few of which are every now and then becoming detached from the rest and roll along'. Wharton Jones made the relatively original observation that it was 'principally in the radicles of the veins that they accumulate in such numbers as to line the

walls of the vessel like epithelium'. He then discusses the work of Poiseuille, noting that it had not involved a distinction between the red and the colourless corpuscles, and the additional findings of Ascherson and Weber, taking issue with Weber's observation that red corpuscles sometimes adhere to the vascular walls and lose their colour.

The question of whether blood corpuscles leave the stream under normal or abnormal circumstances is closely tied up with the question of the nature of the capillary walls. A discussion of these two questions can profitably be deferred to a later chapter.

Bibliography and Notes

1. Harvey's rejection of the direct anastomatic connexions between the arteries and veins proposed by Galen was not made in his *De motu cordis* (1628). There he suggested that the blood might make its way from the arterial to the venous side either through anastomoses or by way of 'porosities' in the solid parts, or both (*in membris et extremitatibus, sanguis, vel per anatomosin immediate, vel meditate per carnis porositates vel utroque modo transit ab arterias in venas*). The same considerations apply to the passage of blood through the lungs. Here Harvey uses the word permeate (*permeare*) and draws an analogy between the passage of blood through the lungs and Nature's production of springs from water which has previously permeated the earth. In the same chapter he states that the right ventricle had to be added when nature wanted the blood to be strained (*transcolari*) through the lungs. (*De motu cordis*, Chapters vii and xi, *Opera Omnia*, London, 1776, pp. 40–57, *passim*.)
2. Harvey now rejects the Galenic anastomoses outright. He had never, he stated, been able to trace any connexion between arteries and veins in the liver, spleen, lungs, kidney or any other internal organ. He had boiled these organs and had shaken or plucked away the parenchyma until he could see every one of the capillary threads (*capillamenta*). He could find no connexion whatsoever between the two systems of vessels. The 'capillaries' to which he refers here are vessels visible to the naked eye, i.e. small arteries or veins. (First disquisition to J. Riolan; *Opera Omnia*, op. cit., p. 105.)
3. Even had the connexions between the terminal branches of the arteries and veins been preserved in Harvey's macerated specimens (which is highly unlikely) he could not have seen them. The true capillaries, i.e. our capillaries as opposed to the small hair-like vessels (visible to the naked eye) formerly given that name, are too small to be seen without a magnifying lens. They were first described by Marcello Malpighi (1618–

1694) in a letter to Borelli written in 1661, four years after Harvey's death. Malpighi made observations on the mesenteric vessels of living frogs with the aid of a simple microscope and was able to see, with some difficulty, he writes, the circulation 'plainly disclosed'. That is, he saw blood enter through arteries that gradually branched until they were too small to be visible and the red colour of the blood itself was lost. Then he saw the blood reappear, now moving in the opposite direction, in small veins that ran together to form progressively larger trunks. The power of the eye cannot be extended further, he told Borelli. He had therefore assumed (presumably following Harvey here) that the blood left the smallest branches of the arteries for the interstices of the tissues and was subsequently picked up by the small veins. Doubt arose, he wrote Borelli, as the result of a chance examination (with a 'more perfect glass') of a dried frog's lung that happened to have retained blood in what he subsequently found were the very smallest vessels, i.e. our capillaries. So great is the extent of these vessels, said Malpighi, that as they proceed from arteries and veins and continue to branch all order with respect to their origin is lost. Only a network of tiny vessels can be seen. It is perfectly plain, he continues, that the blood always stays within this system of minute tubules during this phase of the circulation. It is never poured out into the interstices of the tissues (*nec in spatia effundi, sed per tubulos semper agi*) (*Opera Omnia*, Leyden, 1687, pp. 328, 329).

It should be understood that Malpighi did not see the circulation as a whole in action, as one might stand back and see, for example, the pump-driven circulation of a coloured fluid in a system of pipes all accessible to simultaneous observation. What he saw was as follows: (1) movement of blood in one direction in progressively more finely branching arteries (in the mesentery of living animals); (2) movement in the opposite direction of presumably the same stream in the veins; (3) a gap between, in which he was unable to make out what was taking place, and, finally (4) in the dried lungs of frogs the newly discovered minute blood-vessels. He then inferred that the same vessels were present throughout the bodies of animals.

4. As set forth in an early edition of the *Aphorisms* Boerhaave's concept of inflammation is as follows: Inflammation consists in the attrition of red arterial blood stagnating in the smallest arterial channels. The attrition, or friction, of the particles constituting the blood is a consequence of the force of the blood pressing on from behind in the obstructed channels and gives rise to heat. The process occurs in the small terminal branches of arteries or in the arterial lymphatics. The lymphatics branch off from the arteries and under certain circumstances their orifices may dilate so as to permit the entry of red globules which then become wedged in their narrow channels. Anything that squeezes, distorts or otherwise narrows the conical or cylindrical end of the networks of vascular channels—heat, violent motion, penetrating objects, acrid substances, wounds, contusions, fractures, dislocations—may cause stagnation. So may the clumping of

red blood within vessels to form an obstructing mass. The latter is favoured by sweating, diarrhoea, coagulants and other factors having this action. Inflammation in the broad sense of the term takes place when ever fluids pass from their proper passageways to smaller channels. In the lymph, as in the red blood, there are coarser and finer particles. According to Boerhaave, the true differences between phlegmon (ordinary inflammation with redness, heat, swelling and pain) erysipelas, oedema and scirrhus with inflammation are made plain by these considerations. In phlegmon the obstructed, almost invisibly small arteries become distended, hence redness and swelling. Near-rupture of the smallest fibres constituting the tissues causes punctate pain, the hard resistance of the part is due to compression of solids and liquids resulting from the impetus of blood pressing on from behind, and the friction of blood particles against each other and the narrowed vessel walls causes increased local heat. The cardiac impetus is responsible for local pulsation in the inflamed part, and the swifter return of the blood to the heart as it bypasses the obstructed zone gives rise to the rapid pulse and fever often accompanying inflammation. If the vascular obstruction can be readily overcome an inflammation will terminate by resolution. If not, the fibres of the distended vessels will rupture and discharge their already partly putrefied contents which will then dissolve the softer surrounding solid. The intermingled conglomerate forms the thick, white, glutinous substance called pus (*Aphorismi de cognoscendis et curandis morbis*, . . . Frankfurt, 1710, pp. 81–85).

5. For Spallanzani's observations on the oscillation of the column of blood in the mesenteric vessels of the salamander and his rejection of the theory of vibratile or oscillatory movements on part of capillary vascular walls see his *Expériences sur la Circulation* . . ., trans. by J. Tourdes, Paris, 1800, pp. 193, 262, 263, 269. Spallanzani disagreed with von Haller on a number of points. For some of von Haller's observations see his *Deux Mémoires sur le Mouvement du Sang* . . ., Lausanne, 1756. A description of the axial stream may also be found in von Haller. In the lesser ramifications of the arteries, he writes, 'the more loose colourless particles depart laterally from the more dense and red globules, while the latter keeping on their course more firmly along the axis of the vessel, expel the former laterally and to the circumference' (*First Lines of Physiology*, Edinburgh, 1786. Reprinted with a new introduction by Lester S. King, New York, 1966, p. 109).
6. The views and findings of these three men were widely known. A. P. Wilson Philip's *Treatise on Febrile Diseases*, London, 1799–1802, was translated into German in 1804 and into French in 1819. John Thomson's *Lectures on Inflammation*, Edinburgh, 1813, was translated into German (1820), Italian (1823) and French (1827). Charles Hastings' *A Treatise on Inflammation*, London, 1820, was translated into German in 1822.

7. Ernst Burdach, *Observationes nonnullae microscopicae inflammationem spectantes*, Dissertation, Königsberg, 1825.
8. Burdach, op. cit., p. 9.
9. Karl F. Koch, 'Ueber die Entzuendung nach mikroskopischen Versuchen', *Arch. Anat. Physiol.*, 1832, 6, 121–260.
10. Jean Poiseuille, 'Recherches sur les causes du mouvement du sang dans les vaisseaux capillaires', *Ann. Sci. nat.*, 2nd ser., zoologie, Paris, 1836, pp. 111–15. Poiseuille studied the capillary circulation in the foot of the frog, the mesentery of rats and mice, the tail of salamanders and tadpoles. He described rotatory, translatory and oscillatory movements of the blood globules, making no distinction between white and red globules. His remarks on the axial stream follow: 'If one studies the course of the blood in the veins and arteries of the frog, of very young rats, of the young mouse, one sees, moving from the axis of the vessel toward the periphery, that the velocity of the globules is quite different; the velocity is maximum at the centre; it diminishes to the degree that one approaches the wall: close to the walls one sees a very transparent space occupied ordinarily by serum alone; this space is equal in size to about an eighth or a tenth of the diameter of the vessel. This transparent part of the vessel, glimpsed by Haller, noticed by Spallanzani, in the frog . . . has recently been observed in the same animal by M. de Blainville.' Poiseuille concluded that an immobile layer of serum lined the capillary vessels. When a globule reached this zone its onward movement was arrested. Half in and half out of the zone, globules 'roll, so to speak'. Early in his brief note Poiseuille mentions his belief that the globules are 'endowed with spontaneous movement', but he does not develop this suggestion. He pointed out the possible relevance of an immobile layer of serum lining the capillary wall to Müller's theory of nutrition (i.e. that dissolved fibrin in the serum passed through the vessel walls into the tissues). Poiseuille's elimination of interior friction had some importance with respect to older theories (notably that of Boerhaave) that body heat was generated in this way, and that both the increased local heat characteristic of inflammation and the increased general heat of fever were due to increased velocity of the circulation. Poiseuille does not comment on this, however.
11. Ernst Heinrich Weber, 'Microscopische Beobachtungen ueber die sichtbare Fortbewegung der Lymphkoernchen in den Lymphgefaessen der Froschlarven', *Arch. Anat., Physiol. wiss. Med.*, 1837, pp. 267–72.
12. F. M. Ascherson, 'Ueber die relative Bewegung der Blut-und Lymphkoernchen in den Blutgefaessen der Froesche', ibid., pp. 452–62.
13. Ernst Heinrich Weber, 'Ueber die in den Adern lebender Froesche und Froschlarven sichtbare Bewegung von Koernchen, welche die Gestalt der Lymphkoernchen haben, und ueber die Geschwindigkeit, mit welcher sie sowohl, als die Blutkoerperchen in den Haargefaessen sich bewegen', ibid., 1838, pp. 450–68.

II Addison's Corpuscular Theory

II.1 Earlier Versions of the Corpuscular Theory

The Capillary Walls

Although we have not as yet become acquainted with the full scope of Addison's version of the corpuscular theory of nutritive and inflammatory processes, some attention to earlier versions of the theory will now be appropriate. And since one of the reasons why the theory was abandoned centred on the structure of capillary vessels, we shall enquire as well into developments along this line.

The belief that the basic units, the 'fibres' of the body were themselves built up of globules derived from those found in the circulating blood had adherents in England, France, Germany and Italy in the opening decades of the nineteenth century.[1] The microscope lenses then in use were not corrected for optical aberration. In consequence the microscopist was often misled into taking an optical artifact for a real object. The lenses were good enough to show really existent 'globules' in the blood, but when they were directed at delicate filamentous structures in the tissues, say nerve or connective tissue fibres, an appearance resembling strung pearls might result. Milne-Edwards' memoir of 1823 on the structure of plant and animal tissues furnishes a case in point. It seems indubitable that his 'primary globules' (which he supposed were the elementary structural components of the fibres) were artifacts produced by his uncorrected lenses.[2] The same may be said of the illustrations

published by several English investigators of the time. Home, reporting in 1820 on some findings of Bauer, as well as those of his own, stated that the optic nerve consisted of 'many bundles of extremely delicate fibres, formed of minute globules connected together by a gelatinous substance . . .'. The globules measured from 1/2800 to 1/4000 parts of an inch, 'the size of the red globules deprived of their colouring matter'.[3]

Ignaz Doellinger (1770–1841), who was professor of anatomy at Munich in the eighteen twenties and the head of an important school of opinion, had some closely related views on the subject of the blood globules. In a lengthy paper contributed to the Royal Academy of Sciences in 1820 he presented his findings on the circulation as seen in the transparent fins of small fish and in eggs undergoing incubation. He believed that an active interchange of materials took place between the solid and fluid elements of the blood and those of the tissues. 'It is nothing less than seldom', he writes, 'for one to see a single blood globule passing out of the delicate stream.' After this had happened the globule might return to its source, it might remain in the 'animal mucus' (*Thierschleim*) and adhere thereto, losing its sharp outlines, or it might force its way through the mucus to another vascular channel. Doellinger traced the belief held by some anatomists that blood was always contained within walled channels to an erroneous conception of tissue structure. The tissues were not 'cellular', he wrote, not composed of membranes, threads and spaces, nor of such a nature that the blood would perforce flow in an entirely disorderly fashion if it were to leave the vascular channels. On the contrary the fundamental substance of the tissues was animal mucus. The blood was walled in by the mucus itself, 'just as a stream receives a bed of earth and does not have to be enclosed in a tube'. He has repeatedly made observations that are quite incompatible with the belief (held by Leeuwenhoek, he says) that the finest blood-vessels have walls of their own.[4] Doellinger, incidentally, regarded the blood corpuscles as on the one hand 'animal organisms' or

'infusoria' and on the other as mere parts of a whole.[5] Doellinger's views were shared by many of his disciples.

An important French proponent of the corpuscular theory of nutrition was the physician and physiologist René Dutrochet (1776–1847). In a monograph on the structure and motility of animal and vegetable tissues published in 1824 Dutrochet traced to Robert Hooke the belief (which he himself shared) that muscle fibres were composed of globules strung together like pearls. Leeuwenhoek wrongly failed to accept Hooke's observation, says Dutrochet, but it had been confirmed by Home, Bauer and Milne-Edwards, among others. Dutrochet thought that the solid and fluid components of the body were alike, in that both were composed of a fundamental unit, the globule. Globules in the circulating blood move out from the stream and combine with the tissues . . . 'the vesicular globules contained in the blood add themselves to the tissue of organs and fix themselves there for growth and repair, so that nutrition consists in a veritable *intercalation* of cells all of an extreme minuteness'. He admits that this opinion may sound strange, but in favour of it is the fact that he has often seen the blood globules pass from the circulation and become arrested and fixed in the tissues. 'I have often been a witness of this phenomenon which I was very far from suspecting, while observing the movement of blood in the quite transparent tail of the young tadpole . . . while observing the movement of the blood I have many times seen a single globule escape laterally from the blood vessel and move in the transparent tissue . . . soon after the globule ceases to move and remains fixed. . . .' How did the globules escape from the vessels? Dutrochet asked. Perhaps the vessels had lateral openings, or perhaps the globules were arrested because they reached channels too small to permit their passage. In any case, said Dutrochet, the phenomenon was incontestable and it explained the role of the blood globules in nutrition.[6] It is a bit odd that he called the phenomenon incontestable, since his second explanation would seem to negate its occurrence. He returned to this second explanation after more than a decade.

Because of Dutrochet's claim of 1824, regarding the outward passage of blood globules, he has, like Addison, been hailed as one of Cohnheim's forerunners.[7] But in 1837 Dutrochet himself retracted his claim that blood corpuscles passed out of the bloodstream into the tissues.[8] In the meantime he had published his studies on endosmosis and exosmosis, i.e. the differential passage of fluids of different chemical constitution across membranes.[9] They were to have great importance in physiology, since all exchanges between the blood and the tissues would come to be regarded as osmotic transfers across semi-permeable but continuous membranes. His own work on osmosis, the increasing preponderance of opinion in favour of the existence of true vascular walls even in the smallest blood-vessels, and the disfavour into which the corpuscular theory of nutrition fell in the eighteen thirties (in part due to the introduction of better lenses) probably influenced Dutrochet to take this step.[10] In any case, referring to his observations of 1824 Dutrochet wrote in 1837 that although he had been led to believe at one time in the passage of globules from the circulation and their subsequent 'intercalatory aggregation' in the organs and tissues, and to hold that these globules constituted the elementary units of all organs and tissues, he now thought all of this inadmissible. 'I have seen, it is true,' he writes, 'the blood globules suspend their movement often enough and remain fixed in the transparent organic tissue of the tadpole's tail, but this probably proves that these globules were engaged in very tiny vessels; it was not a phenomenon of nutrition or growth.'[11]

In 1833 Müller, in his *Handbuch der Physiologie*, threw the weight of his authority against the corpuscular theory of nutrition. Nutrition is not a process visible under the microscope, he wrote. The observations of Doellinger and Dutrochet on the outward passage of blood corpuscles had not been verified. Nutrition, according to Müller, consisted in the outward passage of dissolved constituents of the blood—protein, fat and inorganic substances—into the tissues, where they were worked up into new substances,

some of which had not been found in the blood. The most important components concerned were protein and dissolved fibrin. The blood corpuscles remained within the stream.[12] What Müller had to say about the nature of the capillary walls is important in this connexion, for we have seen that the corpuscular theory depended on the belief that the ultimate vascular channels had no walls. In the first (1833) edition of the *Handbuch*, Müller says that from Malpighi to Doellinger it has been the general experience of investigators that in the living animal no membraneous wall is visible in capillaries seen under the microscope. He lists C. F. Wolff, Hunter, Doellinger, Gruithausen, Baumgaertner, Wedemeyer, Meyen and Oesterreicher among those who deny that such membraneous walls exist. On the other hand, Leeuwenhoek, Haller, Spallanzani, Prochaska, Bichat, Berres and Rudolphi claim that fine, invisible walls are in fact present. In Müller's opinion there is direct evidence for the existence of capillary walls. Maceration of the choroid, iris and ciliary body has revealed, he says, that capillaries in these localities are equipped with their own walls; the tiny vessels can in this way be obtained isolated from surrounding tissue substance. Windischmann has demonstrated walled capillaries in the spiral organ of the bird's ear. After stating the evidence in favour of the walls, Müller rather unaccountably closes with the remark that 'in general one must think of the capillary vascular walls as mere thickened margins of the substance, not however as very self-sufficient membranes'.[13] It was on this sentence, in the English translation of Müller's book, that Addison seized in support of his own ideas. The second edition (1835) is unchanged on this point, but in the edition of 1844 (the 4th) Müller's position is unequivocal. He states that the 'capillary vessels are not mere channels in the substance, they also possess membraneous walls'. Not only can these walls be demonstrated in some instances by maceration procedures, Schwann has shown how the capillaries arise from the fusion of cells to form their walls.[14]

With respect to English opinion on the capillaries a case

in point is found in J. W. Earle's article, 'On the Nature of Inflammation', published in 1835 in the same journal that was a few years later to carry Addison's first papers on the subject. In this article Earle approved the view (which he attributed to Wedemeyer) that capillaries were membraneless canals or channels in the tissues, like 'brooks in the moist earth'. He does so for several reasons, one of which is the 'facility with which single globules . . . quit the stream and penetrate among the ultimate globules that constitute the surrounding texture, and with which other globules are seen to quit this texture and enter into the venous current. . .'.[15] The statement is of a kind with which we are now familiar. Earle (no more than Dutrochet at an earlier date) did not distinguish between red and white globules or corpuscles in the blood. A few years later the new view is in evidence. In James Paget's authoritative review of 1842 on the microscopic structure of the tissues, we find that the capillaries are said to have 'distinct walls'. They are not 'mere channels drilled in the tissues around them'. Citing Henle's textbook of general anatomy as one of his sources, Paget says that the capillaries or smallest vessels 'are composed of a completely structureless membrane, in which no fibres or striae are ever discernible, but which bears minute oval corpuscles, the persistent nuclei of the cells from which the capillaries are formed'.[16] By the time Addison began to publish this view of the matter, it had won general sanction.

It was mentioned above that Addison had been immediately preceded by Martin Barry in the revival of the corpuscular theory. The ideas of the two men were close but they by no means coincided. By 1840 Barry was aware of the work being done by such men as Schleiden, Schwann and Valentin on the continent and he attempted to link his own investigations in the fields of embryology and haematology with theirs.[17] Barry's observations of developing tissues in the animal embryo led him to agree with Schwann and others that globular or corpuscular bodies regularly combined to form tissues and organs. The 'corpuscular

bodies' of Schwann were of course cells of various sorts, but it was the peculiar claim of Barry that the 'corpuscles' seen to enter into combination in the formation of tissues were identical with those circulating in the blood. 'Every structure I have examined,' he writes, 'arises out of corpuscles having the same appearance as corpuscles of the blood,' including cellular, nerve and muscle tissues, the crystalline lens, even the spermatozoon and the ovum. And by blood corpuscles he means those which, viewed singly, have a 'transparent yellow colour', i.e. the red corpuscles.[18] As did Addison, Barry thought that pus corpuscles, mucus corpuscles and certain of the corpuscles in the blood were identical in appearance and origin. They represented the 'nuclei' of the red corpuscles. This seems to be related to Addison's belief that they were formed by a stripping-off of the outer corpuscular coat. Barry did not discuss the passage of corpuscles from the blood to the tissues, but this would seem to be a necessary correlate of his theory. He specifically rejected Schwann's claim that pus cells, mucus cells (as all cells) formed out of a cytoblastema.[19] In Barry's scheme of things the red cells are the protagonists, in Addison's the white cells. Barry credited Addison with 'the discovery of an immense number of colourless globules' at the top of coagulating blood, another indication of the marginal position held by white corpuscles at this time. Finally, in calling Barry's theory a revival of the corpuscular hypothesis we should not lose sight of the fact that his 'globules' were not the optical artifacts seen by Milne-Edwards and others at an earlier time, before the introduction of optically corrected lenses.

Bibliography and Notes

1. Cf. Louis Mandl's *Anatomie microscopique*, Paris, 1848–57, vol. 2, p. 4, where Doellinger and his school in Germany, Home and Bauer in England, Della Chiaje in Italy and Dutrochet in France are mentioned among the proponents of the corpuscular hypothesis, those who

'construsaient les corps avec de globules de sang, mis en mouvement dans les lacunes sans parois de la substance'.

2. H. Milne Edwards, *Mémoire sur la structure élémentaire des principaux tissus organiques des animaux* (Thesis, Paris, 1823).
3. Everard Home, 'Microscopical observations on the following subjects. On Brain and Nerves; showing that the materials of which they are composed exist in the blood', *Phil. Trans. R. Soc. Lond.*, 1821. (Croonian Lecture, 7 December 1820.)
4. Ignaz Doellinger, 'Vom Kreislauf des Bluts' (*Denkschriften der Akademie der Wissenschaftler zu München für die Jahre 1818–20.* Bd. VII, pp. 169–228) especially pp. 191–97.
5. Ibid., p. 225.
6. René Dutrochet, *Recherches anatomiques et physiologiques sur la Structure intime des Animaux et Végétaux, et sur leur Motilité*, Paris, 1824, cf. pp. 164–69, 172, 214–16. It is interesting, in view of the name 'wandering cells' that the white blood corpuscles were to receive from von Recklinghausen in the eighteen sixties, that Dutrochet says of his globules . . . 'ce sont des cellules vagabondes qui finissent par se fixer et par se joindre au tissue des organes' (p. 216). But Dutrochet neither referred specifically to white corpuscles nor did he attribute the movements of the 'vagabond cells' to their own activity, as did von Recklinghausen (cf. Ch. III.4).

   On the subject in general see C. F. Nasse (in Wagner's *Handwoerterbuch*, op. cit., vol. 1, pp. 75–220), who offers the following résumé on pp. 214–16. 'According to Leeuwenhoek's opinion the blood corpuscles serve for nutrition; Doellinger and Dutrochet believed that they could support this opinion (already rejected by Hunter) with microscopical observations, in that they have supposedly seen the occasional attachment of blood corpuscles to the vascular walls. Koch and Müller also describe the manner in which blood corpuscles sometimes reach the parenchyma and adhere there. Baumgaertner and Wagner, on the other hand, explain the phenomenon as follows: a blood corpuscle arrives and remains lodged in a narrow capillary which is stretched by tension and so invisible. This explanation is certainly the correct one, for it is not conceivable that a blood corpuscle can pass out of a completely closed vessel into the parenchyma or why, if nutrition depends on the blood corpuscles, this phenomenon is not more frequently seen. Formation can take place from the plasma alone . . . the blood corpuscles stand in direct relationship to this process only insofar as they yield up dissolved substances in the capillaries or are themselves dissolved. But it is probable that in the capillaries they yield up nothing more than oxygen, which does not itself actually contribute to the formation of organs but only helps to form carbon dioxide, lactic acid, water and extractives.' Nasse then discusses Barry's work of 1840 (cf. note 18) on the development of foetal organs from blood corpuscles and concludes that Barry has been misled. Nasse's opinion on the subject of nutrition is that no additional

proof is needed that plasma occupies the central role in the nutritive process, but the assumption that fibrin (*Faserstoff*) is the sole formative substance does need further examination. The plastic power of fibrin is manifest, he writes, in clotting blood and in the buffy coat of inflammation or pregnancy. The absence of fibrin in the blood of starving animals and its increase in the blood of pregnant women points further in that direction, but Nasse finds it puzzling that the blood of carnivorous animals contains less than that of herbivorous ones.

7. Arnold Rice Rich, 'The place of R.-J.-H. Dutrochet in the development of the cell theory', *Bull. Johns Hopk. Hosp.*, 1926, **39**, 330–65. Rich claims that Dutrochet 'maintained that growth consists in the formation and expansion of new cells', 'originated the term "wandering cell"' and 'first observed the motility and migration of the leucocyte'. It is evident that he was led by his own knowledge of pathology to assume that Dutrochet must have been referring to leucocytes. Before Rich, Dutrochet's observations were recalled by A. Horvath in 1884. His praise was even more extravagant. Referring to the diapedesis of white cells he writes that 'the honour of this discovery attributed to Cohnheim belongs in all justice to the celebrated Dutrochet who, some sixty years ago (in 1824), consequently well before Waller and Cohnheim, observed and described the emigration of blood globules and their penetration into the tissues of organs with a precision and clarity that leaves nothing to be desired'. He quotes the passage on p. 214 of Dutrochet's *Recherches* and says that Dutrochet's description is in some ways superior to modern ones ('Sur l'histoire de la découverte de la migration des globules blancs du sang', *C. r. hebd. Séanc. Acad. Sci., Paris*, 1884, **99**, 1161–63). As did Rich, Horvath overlooked Dutrochet's later disclaimer of the supposed observation.
8. René Dutrochet, *Mémoires pour servir à l'Histoire anatomique et physiologique des Végétaux et des Animaux*, Paris, 1837.
9. René Dutrochet, *Nouvelles Recherches sur l'Endosmose et l'Exosmose*, Paris, 1828.
10. Some comments of Rudolph Wagner made in 1839 or thereabouts are pertinent here. He states that 'nutrition in the vascular parts is effected by plasma transuding the parietes of the peripheral vessels and so bathing the islets of parenchyma directly', although at an 'earlier period it was supposed that the blood globules were deposited entire, and growth and nutrition effected in this way; or otherwise that the nuclei of the blood discs or the blood discs themselves, became aggregated like strings of beads in order to form particular tissues'. Wagner then calls attention to Doellinger's publications on the subject and adds that 'no observer since who has made use of a good microscope has been able to see anything of the kind'. To which Willis, his translator appended the following: 'This was the case till the present year (1842) which has witnessed a revival of Doellinger's notions by Dr. Martin Barry, who appears inclined

to view the blood disc as the immediate agent in the construction of many of the tissues . . .' (*Elements of Physiology*, by Rudolph Wagner, trans. with additions by Robert Willis, London, 1841, pp. 447–48).

11. Dutrochet, *Mémoires*, op. cit., pp. 502–3. Dutrochet still believes that animals and vegetables are composed of cells or 'agglomerated utricles' and that growth must occur by the addition of new utricles, but the 'mécanisme de cette addition qui constitue la nutrition, n'est pas encore connu'.
12. Johannes Müller, *Handbuch der Physiologie*, Coblenz, 1833, vol. 1, pp. 341–45. Müller says that in the nutritional process materials passing from the blood to the tissues are assimilated as soon as they arrive there, while in the inflammatory process assimilation is hindered or stopped altogether and materials accumulate. Inflammation, as Müller understands it, is a pathological alteration of the interchange between blood and tissues, brought about by injury and tissue breakdown, and associated with an 'organic activity' that tends to neutralize the destructive process. Sometimes it succeeds, sometimes it does not (p. 219).
13. Müller, *Handbuch* (1833), p. 207.
14. Müller, *Handbuch* (1844), p. 175.
15. J. W. Earle, 'On the nature of inflammation', *Lond. med. Gaz.*, 1835, **16**, p. 8.
16. James Paget, 'Report on the results obtained by the use of the microscope in the study of human anatomy and physiology', Part I, *Brit. for. med. Rev.*, 1842, **14**, 259–96. Paget was at the time Demonstrator in Morbid Anatomy at St. Bartholomew's Hospital in London. His report is detailed, concise and replete with references to the literature, both old and recent. Paget paid especial tribute to Jacob Henle's *Allgemeine Anatomie* (Leipzig, 1841). With respect to blood corpuscles (by which he means only the red) Paget says that in birds and the lower vertebrates these corpuscles are nucleated cells with colouring matter lying between the nucleus and the external elastic membrane. As for mammals, Valentin, Wagner and Gulliver (according to Paget) regard the central zone of red cells as an accumulation of colouring matter. Henle believes that nuclei are present in young red cells only. Paget then discusses at some length Martin Barry's claim that the central disc of the red cell contains a coiled filament of the same character as the fibrils found in muscle and other tissues, finding it unproved. Of the corpuscles in lymph and chyle, Paget states that 'some of them are generally discernible in the blood, moving, as it circulates in the capillaries, in the peripheral portion of the current'. (We see that for Paget the white cells are not necessarily an intrinsic part of the blood.) Citing Henle's *Allgemeine Anatomie*, p. 491, Paget holds that the capillaries (or finest blood-vessels) 'are composed of a completely structureless membrane, in which no fibres or striae are discernible, but which bears minute oval corpuscles, the persistent nuclei of the cells from which the capillaries are formed. . . .

This may be named the primary vascular membrane.' Paget also cites Poiseuille, Weber, Wagner and Ascherson on the phenomenon of axial flow in the small vessels.

17. Martin Barry, 'On the corpuscles of the blood', *Phil. Trans. R. Soc. Lond.*, 1840, 519–612. Cf. pp. 604–8. Barry cites Valentin's description of the formation of muscle fibres from groups of 'globules' and suggests that these globules 'may really have been blood-corpuscles'. On p. 608 Barry states that we are 'indebted to Schwann for the discovery that all elementary parts of organisms have a common principle of development' (note that he sees Schwann not as the discoverer of the cell but as the discoverer of a principle). Barry finds that 'objects all having the same colour, form and general appearance, namely, the corpuscles of the blood, enter immediately into the formation of tissues. . . .' The reference is of course to red corpuscles.
18. Ibid. (London, 1841), pp. 201–68, cf. pp. 217, 218. On p. 218 Barry states that 'every structure I have examined arises out of corpuscles having the same appearance as corpuscles of the blood', including not only cellular, nervous and muscular tissues but the crystalline lens, the spermatozoon and the ovum as well. Viewed singly the corpuscles have a 'transparent yellow colour', but seen *en masse* they give the blood its red hue.
19. Ibid., pp. 219–21. Barry points out that, according to Schwann, pus cells are cells formed in a cytoblastema exuding from the blood-vessels in greater quantity and altered quality during the course of inflammation. (The subject is discussed in Schwann's *Mikroskopische Untersuchungen*, op. cit., p. 79.) Barry states that in his opinion the pus corpuscle forms from the nucleus of the ordinary blood corpuscle, and, since Henle and Mandl admit that pus corpuscles and mucus corpuscles are identical, it appears to him that mucus corpuscles, too, are derived from blood corpuscles (pp. 221, 222). Barry, we see, did not accept Schwann's idea that cells arose *de novo* from the blastema. He states (p. 203) that 'young cells originate only through division of the nucleus of the parent cells, instead of arising as a sort of product of crystallization in the fluid cytoblastema'. It is possible that Addison derived his ideas on the subject (which were not expressed until 1843) from this source. Some remarks made by Barry about the cell nucleus have, if taken uncritically, a prophetic sound. He notes that according to Schleiden the nucleus is cast off as useless once the cell is formed (i.e., the cell as outer sheath), while according to Schwann the nucleus never produces anything, with the exception of fat droplets in fat cells. But in his own opinion 'the nucleus is the source of new substance, not only of the transitory contents of its own cell ("Zellinhalt" of German authors), but also of the two or three principal and last formed cells destined to succeed that cell' (pp. 202 207).

II.2 Part I of *The Actual Process of Nutrition* (1844)

Critical reception of Addison's Ideas in England

In his previous writings Addison had put forward, although briefly, the leading ideas on which his new theory of nutrition and inflammation was based. In the essay that we are about to examine these ideas are expounded in more detail. Its first part appeared in 1844 in the *Transactions of the Provincial Medical and Surgical Association*. It was also published separately, bound with a second part, which was dated 1845.[1] Since the second part contains a criticism of the blastema theory directed against John Hughes Bennett's treatise on inflammation and nutrition (1844), it will be convenient to defer consideration of this part to the next section of the present chapter. Here we shall confine ourselves to the initial half of the essay and to the critical reception given Addison's ideas in England after its appearance.

Addison begins the essay with a review of his already published work. He says that his interest had originally been solely in the mode of formation of the buffy coat but that it had gradually expanded to include 'the wider sphere of nutrition, secretion and disease in general'. He had reached the conclusion that lymph and pus globules, 'exudation' cells and epithelium originated alike from colourless corpuscles in the circulating blood, that the colourless corpuscles were more abundant in blood drawn from vessels in inflamed zones, and that fibrin never gave rise on clotting to corpuscles or globules of any kind. One of the chief difficulties in establishing the theory that he desires to propose is the doctrine that the smallest blood-vessels have permanent tubular walls, and he now intends to show their true nature as well as the manner in which colourless blood corpuscles come to be included in their structure.[2] But before doing so he has some additional experiments to report, designed to demonstrate further resemblances between pus corpuscles, mucus corpuscles and colourless blood corpuscles.

We recall that in 1842 Addison had been taken to task by Wharton Jones for stating that the buffy coat was formed by the coalescence of the colourless corpuscles in the blood. Addison had denied the charge, although on rather shaky grounds. But now we find him returning to his original opinion or to one very close to it. Microscopic observation of the upper layer of 'inflammatory' blood before coagulation takes place has now convinced him that the white corpuscles disintegrate during coagulation. They are resolved into 'molecules' and it is from these molecules or disintegrated corpuscles that 'fibrinous filaments shoot out on all sides, as from so many centres'. Addison now thinks it highly probable that all of the molecules met with free in the blood, as well as the 'plastic fibrillating liquid' of the blood are derived from the interior of the white corpuscles.[3] Neither the fibrin of the blood nor the serum (the fluid seen in fully clotted blood) are present as such in the circulating fluid. Instead, both are enclosed within the colourless blood corpuscles. What then is the nature of the fluid in which the corpuscles move? Addison has no answer, since this fluid cannot be procured without causing the rupture of at least a few of the corpuscles.[4]

It is still common today for physiologists to call the blood, somewhat metaphorically, a 'tissue'. This expression originated early in the nineteenth century, but its meaning was then much stronger and more literal. Addison, Gulliver and many others, probably the majority of investigators at the time, thought of the blood as a fluid 'potential' tissue; the buffy coat or inflammatory crust, on the other hand, was an actual tissue, occupying the same level as the other tissues making up the structure of the animal body. Addison calls the fluid that appears briefly at the surface of inflammatory blood after it has been drawn and allowed to stand a 'plastic fluid'. When this fluid fibrillates, following the disintegration of its white corpuscles, 'it incorporates the molecules and unruptured corpuscles, forming tissue'.[5] While still within the body the circulating tissue may leave the blood-vessels and in the same way become incorporated into the solid structures.

If this is true of the white corpuscles in the blood it ought also be true, to one degree or another, of pus and mucus with their content of corpuscles derived from the blood, hence the series of experiments that Addison is about to report. He added *liquor potassae* and acetic acid to the latter two fluids, observed the disintegration and disappearance of their corpuscular content and thought that he could detect the development of an abnormal counterpart of the 'elastic fibrous tissue' formed when blood underwent coagulation. Mucus and pus corpuscles were nothing more than altered colourless corpuscles and the 'glairy fluid termed mucus is nothing more than an altered state of the fibrillating *liquor sanguinis*'. The colourless blood corpuscle is fundamentally a secreting cell, therefore Addison sees no difficulty in the supposition that 'similar living cells . . . form not only sundry kinds of fibrous or mucous tissue, but the tears, milk and bile' as well.[6] He thinks now that the evidence points away from Barry's claim that the molecules and granules within the white blood corpuscles and free in the blood are young cells being formed within parent cells, toward the likelihood that there is a gradual rise in the scale of organization beginning with 'primary' colourless cells (originating in the chyle of the intestinal villi, he says). They pass through several generations of change to become red cells, and then, once again, white cells ('secondary', presumably). The white cells 'form the foundations of the tissues and the special secreting cells—the link between the blood and the more solid structures, the unit from which these pluralities rise'.[7] We may recall here that in 1841, before Addison began his gradual break with the blastema theory, 'fibrin' was his link between the solid and the fluid components of the body.[8]

Addison now fulfils his earlier promise to review the doctrine that blood-vessels have 'permanent tubular coats', in relation to his theory of nutrition and inflammation. In the course of normal nutrition, he writes, the colourless blood corpuscles first adhere to the margins of the vascular channels. They then pass into and become part of the tissues constituting their boundaries. Some of them move

beyond to free surfaces, where they become epithelial cells. Others remain in the depths of the tissues and yield up a variety of secretions, usually accompanied by corpuscular dissolution. In abnormal nutrition (which includes inflammation) the colourless blood cells adhere and pass out as before, but in far greater numbers. They are subsequently thrown out on free surfaces as the cellular components of purulent and mucus fluids. Others become imperfect or abnormal epithelial cells. The fibrillar margins of the capillaries are 'formed by the fibrillation of the *liquor sanguinis* contained in the interior of the colourless blood corpuscles, some of the corpuscles being expended in forming the fibrous tissue, others passing through it in the interstices of the fibres for further elaboration into epithelium'. To give additional clarity Addison states that the buffy coat or inflammatory crust is to the underlying red clot as the 'wall' of the capillary vessel is to the blood flowing within its bounds.[9]

At this point Addison attempts to separate his facts from his hypotheses. He admits that he has offered a *theory* of nutrition, and that medical theories are rightly viewed with suspicion. But the facts are these: (1) colourless corpuscles are constantly present in the circulating blood, and are particularly abundant in vessels actively engaged in nutrition and inflammation; (2) these corpuscles become attached to the margins of small vascular channels in the frog's foot, their number increasing sharply when the tissues are irritated or injured; (3) the corpuscles contain within both 'molecules' and a plastic fluid capable of forming fibres; (4) colourless corpuscles and molecules are seen in growing membranes, in the walls of blood-vessels, in the buffy coat and in the mucus; (5) there are observable transitional forms between colourless blood corpuscles and all varieties of lymph and pus corpuscles and exudation and epithelial cells. To supplement these facts—since the actual events of nutrition and inflammation cannot be followed visually in all their details—it is necessary to hypothesize that (1) some of the adherent colourless corpuscles form the vessel margins by first

disintegrating and then giving rise to fibrils; (2) others become incorporated in the vascular walls and adjacent tissues; (3) if nutrition be hurried or abnormal some of the colourless corpuscles become pus and 'exudation' corpuscles.[10] It is interesting, in view of the usual ascription to Addison of the discovery of white cell diapedesis, that he himself classifies the passage of colourless cells through the vascular parietes as hypothesis rather than fact. He has *not* seen it take place. The reason is, he writes, that here as in other instances the nutritive processes take place too slowly to be followed by the eye.[11] In closing this section of the essay Addison contrasts his own belief that 'the globules of the blood are the sole agents of nutrition' with that of the celebrated organic chemist, Justus Liebig, who holds that 'the globules of the blood take no share in the process of nutrition'.[12]

The critical reception accorded to Addison's exposition of his new theory of nutrition and inflammation is of great interest to us, for it will show precisely where the theory came in conflict with what was generally agreed to be the true state of affairs. And it is just this that we must grasp if we are to bring our thoughts in harmony with those prevailing at the time. The reception of his views, as might be expected, was for the most part unfavourable. The critic of Addison's paper on inflammation and the origin of tubercles in the lungs (*Transactions*, 1843) casts doubt in the first place on the technical aspect of his work. Some of Addison's findings were of value, said the reviewer, but others would not 'stand the test of further investigation, particularly with a microscope of qualities superior to that which we understand Mr. Addison to have been using'.[13] Addison had done well in calling attention to the colourless corpuscles of the blood, for these 'on account of the correspondence in size and outline to the red discs are very apt to escape notice'.[14] He agrees with Addison that the fibrous arrangement presented by fibrin during coagulation is the paradigm for the development of fibrous tissue in the tissues of the body itself. That is, 'the simple coagulation of fibrin in this form is the origin of the ordinary fibrous tissues'. More-

over, he points out, this view is sanctioned by the work of Gulliver and Carpenter.[15] On the other hand he strongly rejects Addison's equation of colourless corpuscles in the blood with those found in pus and mucus, stating that 'pus corpuscles have something too specific in their *character*, if not in their *appearance* for this claim to be acceptable'.[16]

Addison's experimental studies on frogs have opened a new line of inquiry, the reviewer allows, but they should not be generalized upon until similar experiments have been carried out on warm-blooded animals. But the claim that circulating corpuscles leave the blood to become fixed in the tissues and then transformed into structural elements or secretions is highly unlikely, especially since Bowman and Goodsir have shown that a structureless membrane lies beneath the epithelium of the skin and mucous membranes. It seems to the reviewer 'beyond all probability that cells should be continually escaping from the capillary vessels, passing through the basement membrane and becoming transformed into epithelium cells on the other side', and much more likely that Addison has been misled by the resemblance between all cells at an early stage of their development. The same considerations apply to Addison's views on tubercle: here the reviewer hewed strictly to the blastema line, following the lead of Gerber and Gulliver in stating that 'the essential character of a tubercular deposit is its *unorganizability*, indicated by its granular character and the imperfect formation of its cells', while in pneumonia the 'exuded substance is organizable'.[17]

In the preface (dated 17 January 1844) to the separately published version of the *Actual Process of Nutrition* Addison briefly mentions the above reception accorded his article and remarks that the distinction made by his critic between *character* and *appearance*, on which basis the identification of pus, mucus and blood corpuscles was rejected, is not one that he himself can understand.[18] Addison did not have to wait long for instruction on this point. A few months later the same critic replied with a long review of the first part of the *Actual Process of Nutrition*.[19] This time he makes it clear

that it is Addison's hypotheses rather than his facts that he cannot accept. As for the 'facts', most of them have already been put forward by other microscopists. But he is quite unwilling to agree that Addison has established the identity of lymph and pus corpuscles, and of exudation and epithelial cells, with the colourless cells of the circulating blood. Furthermore, Addison's experiment with acetic acid and *liquor potassae* prove only that the interior of some or all of these cells yields under such treatment a plastic substance of some kind; they definitely do *not* prove, as Addison claims, that all of the plastic matter of blood is enclosed within them.[20] The cornerstone of Addison's theory of secretion, nutrition and inflammation rests on the thesis of the identity of these cells, adds the reviewer, yet surely the similarities of appearance do not allow us to assert similarity of character. Addison might find the same appearance, including the responses to acetic acid and *liquor potassae*, in cells as different in character as those of an oyster and a man.[21] As for Addison's statement that a gradual transition between the colourless blood corpuscles within the blood-vessels and the lymph and pus globules outside of them can be observed, this merely asserts what is to be proved.[22] The reviewer then closes with a sketch of his own ideas as to the relation between the nutritive process and its abnormal variant the inflammatory process.[23]

Addison was much more roughly handled in the same year by a writer in the *Lancet*.[24] After first remarking that to keep fact and hypothesis separate in the practice of microscopy was of the utmost importance for the advancement of science, and that modern achromatic lenses had made this possible, the reviewer went on to say that only when strictly inductive Baconian procedures were carried on by microscopists well acquainted with the current state of knowledge of anatomy, physiology and pathology could success in this field be achieved. Mr. Addison had signally failed. His 'facts' were of two kinds, long known or doubtful. His theories (presented intermingled inextricably with his facts) were such as to be quite irreconcilable with the chemical

views of Liebig, with the findings of Schleiden, Schwann, Henle and Valentin, indeed with the whole series of 'laborious investigations which have lately been carried on by the histologists of Germany'. Had Addison been acquainted with the work of these men, in particular with that of Henle, he could hardly have supposed that the capillary blood-vessels lacked permanent tubular coats. Had he known of Müller's positive proof, making use of frog's blood from which the corpuscles had been removed by filtration, that fibrin was present in dissolved form in the *liquor sanguinis* he would hardly have asserted and attempted to prove that it was contained within the white corpuscles. It would have been better had Addison refrained from 'wild speculation' and taken the time to learn histology under the guidance of some experienced person before involving himself in the study of nutrition, secretion, inflammation and tubercle. 'With this observation,' concludes the reviewer grandly, 'we take leave of Dr. Addison.'[25]

In the above review the name of Charles Williams was mentioned (and dealt with somewhat more courteously) as one whose work had offered some support to Addison. Williams' findings were reported in a treatise on the principles of medicine, published in 1844. He had studied the small blood-vessels of the irritated swimming web of the frog under the microscope and observed the accumulation of adherent white corpuscles on their interior surfaces. In describing these changes he mentions Addison's findings along the same lines, but he offers no support to Addison's claim that the corpuscles leave their channels. Williams emphasized (where Addison did not) the obstruction of flow that presumably resulted when white blood corpuscles accumulated in this fashion. He was also of the opinion that the white corpuscles developed within the capillaries at sites of irritation. They bore no resemblance to the red discs, he wrote, and he doubted that they were the 'nuclei' of these discs as Barry supposed. It seemed more likely to him that they were formed on the spot 'in the plasma or blastema of the *liquor sanguinis* itself'.[26] We recall that

Addison at first spoke, rather vaguely, of a 'development' of the white corpuscles in capillary blood-vessels. Later, as he came to reject the blastema theory, the 'development' of white blood corpuscles of course dropped out.

Addison replied to the unfriendly review in the *Lancet* with a series of articles in the *London Medical Gazette*.[27] He began with the remark that he was 'aware of the hostility which all innovators upon established opinions must be prepared to expect'. He continued with an account of the repetition and amplification of some of his already published experiments purporting to show the transformation of the granular or 'molecular' content of pus corpuscles into fibrous and membraneous tissue, including the 'structureless basement membrane of Mr. Bowman'. He asks his critic to repeat the experiments himself rather than to urge against them the very opinions that these experiments show to be no longer tenable.[28] It is not our aim here to explain or understand (in terms of modern colloid chemistry, say) the peculiar changes produced by Addison's procedures, but only to point out that for him they indicated that 'the fibrous tissue here formed by my manipulations could not by any visible or microscopical character be distinguished from that formed by the fibrillation of the buffy layer of the blood, or by the process of nutrition in the living body'.[29] The penultimate in this series of papers contains a straightforward rejection of the blastema theory. No cell in the body is formed, says Addison, 'otherwise than perhaps by the passing of two cells into one, or the division of one cell into two, an event which may occur during their structural transformations'. And Addison has 'never seen the slightest disposition to the formation of cells in any blood plasma, lymph, blastema, exudation, effusion or *liquor sanguinis* that I have examined'.[30] Here we seem to find the exact equivalent of Virchow's dictum, *omnis cellula e cellula*, *all* cells arise from cells. But it will be eight years before Remak will deny the extracellular origin of animal cells from blastemas and eleven years before Virchow enunciates his dictum. We shall return to this subject in the following

chapter, but a word of warning is in order. It will be well to refrain from awarding Addison the palm, in this respect, until we have examined his later publications.

Bibliography and Notes

1. William Addison, 'The actual process of nutrition in the living structure demonstrated by the microscope; and the renewal of the tissues and secretions, with the phenomena and products of inflammation', *Trans. prov. med. surg. Ass.*, 1844, **12**, 235–306. A separately published version bore the additional designation 'Second Series of Experimental Researches' and was dated 1843. In my copy it is bound with 'The Actual Process . . .' etc., 'Third Series of Experimental Researches' dated 1845 and published by J. Churchill of London. The 'Third Series', i.e. the second part of 'The Actual Process of Nutrition' did not, as far as I know, appear elsewhere in print. The opening paragraphs of the 'Second Series' were expanded in the separately published version into a preface dated 2 December 1843. To this preface Addison appended a note dated 17 January 1844, hence it would appear that the composition of the separately published version post-dates the article in the *Transactions*. The added note is a response on Addison's part to critics of his technical armamentarium. He states that Powel and Lealand had 'fitted one of their very best one-eighth-object glasses' to his microscope, and with his original eyepieces a 'magnifying power of 700 diameters linear' was now at his disposal (op. cit., pp. xv, xvi–xvii).
2. Addison, *Actual Process* (second series), separately published version (op. cit.), p. 3.
3. Ibid., pp. 4, 5.
4. Ibid., pp. 6–8.
5. Ibid., p. 8.
6. Ibid., pp. 11–15.
7. Ibid., p. 21.
8. Cf. Chapter I.1.
9. Addison, *Actual Process*, op. cit., pp. 26, 27.
10. Ibid., pp. 27–29.
11. Addison, *Transactions*, op. cit., pp. 269, 270.
12. Ibid., p. 281.
13. (a) Unsigned review article in *Brit. for. med. Rev.*, 1844, **17**, 91–96, cf. p. 92. In a letter to the *Provincial Medical and Surgical Journal* (1844, **7**, 296), Addison took issue with 'this indefinite but sweeping objection from the unknown editorial WE' and added that as far as he knew the writer of the editorial had never seen his microscope. He then states that a few months ago Powel and Lealand fitted one of their best

one-eighth object-glasses magnifying *750* diameters linear to his microscope (cf. note 1). A letter, signed 'Phylax' (ibid., p. 355) called the reviewer's remarks on Addison 'a most impertinent style of criticism, and a most unfair use of the editorial screen'. Addison, in a later communication (ibid., pp. 457, 458) acknowledged the defence by 'Phylax', gave some additional findings made with the new objective (see 13(b)) which, he now writes, has in combination with his original eye-pieces a magnifying power of 700 diameters linear, and then threw down the gauntlet before the upholders of blastema theory: '*I challenge any microscopical observer to show the formation of pus, or of any other globule, by the exudation or coagulation of the fibrine of the blood*'. While his views on nutrition and secretion are 'quite incompatible with our present physiology', he admits, they 'combine into a compact whole a *new physiology* with the results of pathological anatomy'.

(b) After obtaining the new objectives for his microscope Addison demonstrated his 'molecules' to several witnesses, including the professor of geology and mineralogy at Trinity College, Dublin. In another letter to the *Provincial Medical and Surgical Journal* (5 June 1844, pp. 137, 138; no vol. no. given) Addison states his reasons for believing that his 'molecules' are different from those of Robert Brown (cf. Ch. I, note 14 (c)). Noting first that when a thin film of fluid between two glass laminae is examined under the microscope one sees currents moving in various directions, probably due to evaporation taking place at the edges, he continues: 'Now the active molecules of Brown, and other observers, although they exhibit peculiar and very singular motions, *independent* of, are yet never seen to oppose or *contend against*, this current . . . whereas the active and independent molecules which I can see in the saliva move about rapidly in all directions, at right angles to or opposed to these currents; besides many of the forms are more or less cylindrical, and exhibit a wriggling motion, entirely distinct from anything of the kind to be witnessed in inorganic or dead molecules.' Thus it appears that some of Addison's 'molecules' were micro-organisms. He seems to recognize this, in fact, but he points out that it is of interest 'to determine whether they originate from the active molecules of the mucous cells . . . or from invisible ova in the atmosphere; or . . . from both sources'.

14. Ibid., p. 93.
15. Ibid. (for Gulliver's views see Ch. I.2; for William B. Carpenter's see his *Principles of Physiology*, London, 1842, pp. 452–56.)
16. Ibid.
17. Ibid., pp. 95, 96.
18. Addison, *Actual Process*, op. cit,. pref. p. xix.
19. Unsigned review article in *Brit. for. med. Rev.*, 1844, **18**, 91–114.
20. Ibid., pp. 91–94.
21. Ibid., pp. 98, 99. The reviewer states that he himself has of late been comparing epithelial cells and cancer cells under the microscope. In

some instances he finds that the appearances allow for a distinction to be drawn, in other instances they do not. Yet in both cases, he points out, the cancer cells are distinguished by an extraordinary degree of reproductive power.

22. Ibid., p. 100.

23. Ibid., pp. 101–5. The reviewer had already remarked (p. 91) that the opinion that inflammation was nothing other than an 'altered form of the ordinary nutritive process' was widespread among physiologists and pathologists. This is his own view as well. He suggests that the blood in inflammation acquires an increase in its plastic power (associated with an increase in its content of fibrin and white corpuscles), but a decrease in its formative power (hence the tendency to suppuration and ulceration).

24. Unsigned review in the *Lancet*, 1844, **i**, 586–88.

25. The reviewer's own views are not beyond reproach. He claims that every microscopist since Spallanzani has been acquainted with the colourless corpuscles of the frog, but finds no reason to conclude that their occasional accumulation in inflamed vessels is an essential feature of the inflammatory process. He challenges Addison to provide proof that colourless corpuscles circulate in the blood of man as they do in that of the frog. Many of the capillaries in man, he claims, are too small to admit colourless corpuscles. How then can they accumulate to cause inflammation? But this is not at all Addison's view, although it seems to be that of Williams (see note 26).

26. Charles J. B. Williams, *Principles of Medicine*, Philadelphia, 1844, pp. 212–15. On p. 215 appears Wharton Jones' phrase: the white globules are rolled along by the current 'like pebbles by a rapid stream'. Williams believes that obstruction of the capillaries by white corpuscles is a proximate cause of inflammation. Cooper's *Dictionary*, London, 1872, vol. II. p. 66, notes this and states that Williams 'was not freed from the pathology of Boerhaave and Hunter, and believed that the chief phenomena of inflammation were referrable to obstruction of debilitated capillaries by blood rendered viscid by unusual abundance of white corpuscles, together with increased action of the arteries'.

27. All of these papers bear the title 'On the transformation of pus cells into a mucous or fibrous tissue' and appear in the *London Medical Gazette*, N.S., vol. II, for the Session 1843–44, pp. 650–52; 690–92; 725–27; in vol. I for the session 1844–45, pp. 69–73, 250, 251. The 'synoptical tables' contained in these articles also appear in the separately published version of *The Actual Process . . .*, op. cit. The last in the series points out the close similarity in the chemical composition of mucus and 'protein'. Taking Kemp's figures from the *London Medical Gazette* of 29 July 1842 (mucus $C_{48}H_{39}N_6O_{17}$; protein $C_{48}H_{36}N_6O_{17}$) Addison says that the colourless blood cells, together with mucus and pus corpuscles, can be characterized as 'living cells containing within them a plastic element (protein, if so it be) and living molecules: when the cell

bursts the molecules retain their vitality, but the plastic elements may become subject to chemical laws. . . .' He denies that chemistry alone can solve the problems posed by organic change. In particular, 'neither putrefaction nor fermentation are, strictly speaking, chemical operations; the results indeed come fairly within the province of chemistry, but these results can no more be obtained without cell-life than a secretion'. Within the scope of the term 'cell-life' he includes 'those immeasurably minute, active, and voluntary moving forms, always, as far as my experience goes, to be found in every putrefactive matter'. We see from this that, in the controversy between the adherents of the chemical school (whose chief was Liebig) and the school represented by Schwann in Germany and Caignard-Latour in France (who held that putrefaction and fermentation were not strictly chemical activities, but required the participation of living organisms), Addison was on the side of the organicists.

28. *On the Transformation*, etc., op. cit., pp. 650, 651. Addison also makes the interesting statement (p. 692) that 'new facts' require '*new forms of mental apprehension* appropriate to *their* interpretation'.
29. Ibid., p. 690.
30. Ibid., p. 73.

II.3 Addison's Dispute with Bennett

Inflammation as a form of disturbed tissue nutrition: corpuscle versus blastema.

Until the end of the first quarter of the nineteenth century inflammation had been regarded by most physiologists and pathologists as primarily a disturbance of the circulation of the blood. The various theories put forward to account for inflammation had centred on the nature of the circulatory block presumed to occur. Spasmodic contraction of small arteries (Friedrich Hoffmann) and the impaction of blood corpuscles in channels too small to transmit them (the *error loci* of Boerhaave) were rival accounts from the early eighteenth century. Toward the end of the eighteenth century Cullen's revival of the idea of 'spasm' of the small vessels as the cause of the block, hence of inflammation, enjoyed con-

siderable popularity. The dispute among early nineteenth-century investigators of the microcirculation (Wilson Philip, Hastings, Thomson, etc.) must be understood along these lines. Wilson Philip, for example, had traced the vascular obstruction to capillary 'debility', rather than to spasmodic vascular contraction.

While echoes of this controversy are still to be heard in the eighteen forties, as when Williams ascribes great importance to the obstruction of capillary vessels by accumulated white cells, it is evident that the locus of the controversy has shifted. Where interest formerly lay solely in the vascular system its scope has now broadened to include events taking place in the so-called 'parenchymal' tissues lying beyond the vessels. The 'third estate'—the first two being the blood-vessels and nerves—is about to come into its own. The class of events placed under the rubric of inflammation now not only includes changes taking place in the tissues but, more than this, for an increasing number of pathologists and physiologists the tissue events have become central rather than peripheral to the whole problem of inflammation. From an event to be understood primarily as a circulatory disturbance inflammation has become a complex derangement involving the growth, maintenance and repair of tissues nourished by fluids and dissolved solids passing out from the bloodstream, into which these same tissues discharge their waste matter. And this is what is meant when, in the terminology of the time, inflammation is classified as a 'nutritive', rather than (as formerly) a circulatory disturbance. There were of course differences of opinion regarding the precise character of the disturbance of nutrition involved. Some even held that 'nutritional disturbance' was not an entirely suitable designation, since it was only a certain aspect of this very complex process that was deranged (Johannes Müller and Rudolf Virchow are cases in point). As for Addison, his atypical views on the nature of the capillary walls, his espousal of a modified 'corpuscular' theory of nutrition and his increasing scepticism concerning the blastema hypothesis shifted him further away from the

centre of shared opinions than any other investigator of his time.

The second part of Addison's essay, *The Actual Process of Nutrition* was published in 1845. During the preceding year a monograph by John Hughes Bennett had appeared and Addison was obliged to take it into account. Bennett's monograph, entitled a *Treatise on Inflammation as a Process of Anormal Nutrition*, defined a thesis allied to Addison's in some respects but based on blastema theory.[1] Bennett, too, had what he himself called a 'cellular theory' of nutrition and inflammation. Unlike Addison, he accepted most of what Schwann and other cell theorists had to say concerning the formation of cells from a cytoblastema. Moreover, in establishing his own theory of inflammation Bennett had to show that Addison's rival view was inadequately founded. After examining at some length Bennett's presentation of his ideas and evidence in the above monograph we shall return to Addison and his response in the second part of *The Actual Process of Nutrition*.

What, asks Bennett, is inflammation?—'in all ages the pivot upon which the medical philosophy of the time has revolved'.[2] He has himself been engaged for three years in clinical and experimental studies of this problem and he hopes to be able to show that inflammation can be understood as a 'modification of the functions of nutrition, as explained by the doctrine of cytogenesis', Schwann's doctrine being understood here.[3] As far as the traditional four signs and symptoms of inflammation, redness, heat, swelling and pain, are concerned Bennett remarks that their importance and significance have been greatly exaggerated. They are in fact present only when the affected region is external; they are by no means applicable otherwise. For inflammation 'may attack the lungs, liver, kidneys, etc. and yet one or more of these supposed cardinal symptoms be absent'.[4] The usual sequence of vascular changes visible under the microscope in the irritated capillaries of experimental animals is, according to Bennett, as follows: (1) narrowing of the channels and hastening of the blood flow; (2) dilatation

and slowing; (3) irregular oscillation; (4) complete stoppage of flow in some of the involved vessels; and (5) effusion of *liquor sanguinis* or blood plasma into the surrounding tissues, with or without the escape of corpuscles from ruptured vessels.[5] We note here that Bennett is not impressed by the accumulation of white blood corpuscles on the interior walls of the inflamed capillaries. Nor does he mention the outward passage of white corpuscles hypothesized by Addison. He does state, with reference to both Addison and Williams, that such an accumulation of white corpuscles sometimes occurs, but it is his 'conviction that inflammation, accompanied by complete obstruction, may be frequently occasioned independent of any such phenomenon'.[6]

In his opinion the vascular changes, for so long thought to be central to the problem of inflammation, are mere preliminaries to the essential phenomenon, an 'abnormal exudation of the *liquor sanguinis*', of that process. Vascular changes indistinguishable from those seen in inflammation may be produced by factors as diverse as local heat, emotional disturbances and venous obstruction, but it is only when exudation of blood plasma occurs that inflammation can really be said to be present. Even capillary haemorrhages or the exudation of a fibrin-free 'serum' into the tissues are not proof that inflammation is taking place, for they may occur in association with severe vascular congestion. The essential characteristic of the inflammatory exudate is its content of fibrin, and Bennett thinks that all such exudation occurs through the walls of capillaries or intermediate vessels so delicate in structure as to allow the passage only of a fibrin-containing *liquor sanguinis* or plasma.[7]

What then is the nature of the capillary wall? This question is now crucial. As seen in the rabbit mesentery rendered transparent by dilute acetic acid and examined at a magnification of 500 diameters the wall, says Bennett, appears to be 'composed of a simple, transparent, yet very firm membrane, without the smallest openings, studded at irregular intervals with nuclei of various shapes', as Henle has already shown. These walls constitute a 'membrane by

means of which exosmosis and endosmosis may be effected . . . fine filters subjected to vital laws—retaining the solid corpuscles and allowing only the fluid to transude'.[8] The plasma exuded through the membraneous capillary wall is a blastema. It undergoes organization into cells, more or less in the manner described by Schwann. On the one hand 'exudation corpuscles' and pus corpuscles may be formed in it, on the other the cellular constituents of bony tissue, fibrous tissue and so on.[9] Why such very different cellular transformations take place in the exuded blastema is somewhat of a problem, because 'the blood plasma exuded throughout the body, when first poured out, is, in all tissues, essentially the same'.[10] In Bennett's opinion these differences were determined by local factors (e.g. exudates in the region of bone becoming transformed into bony tissue, as in healing fractures), by the 'vital powers' of the whole organism (as in scrofula and other constitutional diseases), and by the rapidity with which exudation occurs (e.g. pus formation in acute inflammation and fibrosis in chronic inflammation).[11] As for the passage of white corpuscles through intact capillary walls Bennett rejects it utterly. 'It can scarcely be conceived', he writes, 'by anyone who has carefully examined the blood globules on the one hand and the structure of the capillaries on the other, that the former can transude through the walls of the latter without rupture. No one has ever seen such an occurrence.'[12] Not only was the outward passage of blood corpuscles impossible, it was equally impossible for pus corpuscles to pass back into the bloodstream unless ruptured vessels were present.[13]

To sum up, inflammation is a 'peculiar perversion of nutrition'. In healthy or normal nutrition we have (1) a healthy state of the blood, (2) a healthy exudation of blood plasma and (3) the formation of nucleated cells in the exuded blastema to yield fat, bone, muscle, nerve and so on. In that process of abnormal nutrition known as inflammation we have (1) an unhealthy state of the blood, (2) an unhealthy exudation of blood plasma and (3) the formation of nucleated cells in the exuded blastema to yield structures foreign to the

organism, as, for example, purulent matter and scar tissue.[14] In other words, just as Schleiden and Schwann have demonstrated the steps of normal nutrition in plants and animals, respectively, so has he attempted to point out along the same lines how in abnormal nutrition the various products of inflammation come into being.[15]

The second part of Addison's essay on nutrition and inflammation,[16] to which we now turn, adds little to what we already know of Addison's thesis and the supporting evidence. It is chiefly important for its attempted refutation of the rival thesis put forward by Bennett in the *Treatise*. In the course of that refutation Addison breaks more openly and decisively with the blastema hypothesis than ever before. He begins by presenting some clinical evidence that, in his opinion, casts doubt on the identification of blood plasma with a circulating blastema. In the treatment of severe dehydration accompanying cholera it has been found beneficial, says Addison, to inject large amounts of saline solution intravenously. How, if the 'fluid of the blood is a plastic organizable blastema', can 'ten or twenty quarts of salt and water run through it with impunity', how, for that matter, can various unassimilated substances be taken up from the alimentary canal?[17] This is merely to cast doubt on the notion. But Addison has a stronger reason for rejecting the blastema hypothesis. He asserts that no microscopist has ever produced unquestionable proof that such 'highly organized and vitalized forms, as pus cells, really do *form* in exuded plasma'.[18] He has himself repeatedly searched under the microscope for evidence that this occurs, but he has never found it.[19] Furthermore, he has never seen any evidence of cell genesis in plasma contained *within* the blood-vessels, and if the contained fluid 'be not a blastema, then certainly no portion of it exuded through a structureless membrane can be so'.[20] Certainly Bennett himself has not seen this take place, continues Addison. There is nothing in Bennett's treatise that would 'lead the reader to suppose that he had ever seated himself before the microscope and really looked at pus cells forming in the plastic exudation'.[21]

Nor does Bennett present any evidence that cell formation occurs in coagulating blood. Here, where the 'whole progress from the fluid to the fibrous tissue may be watched', where 'if ever cells form in the blood plasma, we might naturally hope to see them', nothing of the sort has been seen under the microscope.[22] On the other hand Bennett has failed to observe something that Addison is quite certain occurs, namely 'the extraordinary accumulation of colourless cells in the irritated vessels of the frog's foot, their adhesion to and incorporation with the capillary walls'.[23]

Each man sees his opponent's mote but not his own beam. Where Bennett stated that no one had ever seen white blood corpuscles pass through intact capillary walls to become pus corpuscles Addison could only reply that no one had ever seen pus cells, or cells of any kind, form in a blastema. He could *not* reply, I have seen it! For by his own admission his belief was hypothetical. He can only describe, once again, what he 'sees' in the irritated vessels of the frog's foot —'colourless cells isolated, free, and in motion in a fluid, becoming stationary and incorporated with the solid texture'.[24]

From his own evidence and arguments Addison concludes that the 'physiological doctrine, *that the fluid of the blood is an organizable blastema, holding in solution all the principles essential to the constitution of the textures and secretions* must be abandoned' (his italics).[25] Contrary to the claim made by Liebig and his followers that animal or vegetable protein passes more or less unchanged into the blood, and from there into the tissues, Addison found it far more likely that 'no material whatsoever can take any essential share in the nutrition of the textures, or in the secretions of the living organism, without passing through the structures of at least one species of living cell peculiar or appropriate to the organism. . .'. This, he said, 'I take to be the meaning of what is called *elaboration or assimilation*'.[26] And pus cells, far from being the 'product of diseased action, are really the nutritive particles of the blood, containing within them those stores of living matter from which the solid textures and the

secretions are, or ought to be, reproduced'.[27] He believes that the nutrient materials brought by the blood to the tissues are not present in solution in the plasma but are instead contained within the white cells, where they have been worked up to an assimilable product.[28]

What, then, can be said of the relationship between nutrition and inflammation? The inflammatory process is at the same time a nutritive process, although a perverted one, replies Addison. With respect to the role of the blood-vessels in inflammation and nutrition, it 'must be borne in mind, that where the process of nutrition is actually going on, *there* the vessels are capillary; and capillary vessels are channels running in a determinate manner around and among little fixed islets of living tissue . . . take away the islets and no vessels remain'.[29] In the course of normal nutrition the white cells, at first free in the circulating blood, become stationary. They are then linked together by a plastic matter and fibres that they themselves produce. Subsequently they develop into various cell forms, or their contents are elaborated into various products of secretion. In this way the solid tissues of the body are built up, maintained and repaired after damage or loss. In the abnormal form of nutrition known as inflammation the change of white cells into solid tissues and into secretions is hampered. The vascular channels become blocked and secretory activities deranged. If the untransformable cells continue to accumulate an abscess is the result.[30]

Bibliography and Notes

1. John Hughes Bennett, *Treatise on Inflammation as a Process of Anormal Nutrition*, Edinburgh, 1844.
2. Ibid., p. 10.
3. Ibid., p. 10. On p. viii Bennett states that in the summer of 1843 he laid his views before leading members of the Royal College of Physicians in Edinburgh, and that the 'facts from which they are derived also, were then demonstrated under a series of achromatic microscopes'.
4. Ibid., p. 4. Addison, too, distinguished mere congestion of blood in capillaries from that 'accelerated', 'exalted' and abnormal process of

nutrition known as inflammation (*Actual Process*, 1843, op. cit., pp. 58, 59).

5. Bennett, op. cit., pp. 28–29. In a note on p. 43 Bennett states that he employs '*liquor sanguinis*' and 'blood plasma' synonymously, 'understanding by them the fluid portion of the blood composed of fibrin dissolved in serum'.
6. Ibid., p. 34. Cf. Ch. II.5, note 31.
7. Ibid., pp. 37–40. The older concept of inflammation, centring on the vascular changes, put exudation into the category of 'terminations' of inflammation. But this made it impossible to separate inflammation from mere congestion (p. 40). Hence Andral called inflammation a merely metaphorical term with an interpretation so arbitrary that it should be dropped and the term 'hyperemia' employed in its stead (ibid., p. 76).
8. Ibid., pp. 24–27. Bennett ascribed the vascular changes to an 'increased mutual attraction between the blood and the surrounding parenchyma'. In this way he thought that he could best account for the 'gradual approach of the blood corpuscles to the sides of the vessels; the encroachment on the lymph spaces and the subsequent stoppage, the effusions and exudations where the fluid portions of the blood are drawn through the capillaries, sometimes causing them to crack, and the blood corpuscles to extravasate'. He admitted that this was hypothetical. It should be regarded as only a 'short mode of expressing facts, in the same way that we make use of attraction and repulsion to express electrical phenomena, or of gravitation to explain a variety of physical facts' (ibid., pp. 35–36).
9. Ibid., p. 49.
10. Ibid., p. 72. One of the few to make the assumption that the circulating blood contained a diversity of blastemas in certain diseases, each blastema characterized by a specifically 'diseased' protein, was Carl von Rokitansky, in his *Handbuch der allgemeinen Pathologie*, Vienna, 1846, pp. 495–555.
11. Bennett, op. cit., pp. 73–74.
12. Ibid., p. 38.
13. Ibid., p. 67. To explain the formation of metastatic or secondary abscesses Bennett suggested that small fragments of pus corpuscles might be resorbed into the bloodstream and thus contribute, after re-exudation, to the formation of pus at a new site. Where lacerations of blood-vessel walls were present whole pus corpuscles might re-enter the blood, later to become lodged in capillaries at various points in the body and so to cause inflammation and suppuration. Bennett quotes Zimmermann on this subject with approval (citing a translation of Zimmermann's work in the July 1844 issue of the *Brit. for. med. Rev.*) although he did not of course agree with Zimmermann on all points (ibid., p. 69).
14. Ibid., p. 77.
15. Ibid., pp. 77–78.

16. William Addison, *The Actual Process of Nutrition in the Living Structure*, London, 1845, bound with the first part.
17. Ibid., pp. 50–55.
18. Ibid., p. 55.
19. Ibid., p. 36.
20. Ibid., p. 61. In the same passage Addison criticizes Carpenter for claiming (as he himself had only a few years before) that some of the white corpuscles seen on the interior walls of irritated small vessels were generated on the spot from the contained fluid.
21. Ibid., p. 56.
22. Ibid., p. 62.
23. Ibid., p. 57.
24. Ibid., p. 85.
25. Ibid., p. 66. Addison had already stated his belief that cells arose only by division of pre-existing cells. Cf. ch. II.3.
26. Ibid., p. 73.
27. Ibid., pp. iii, iv.
28. Ibid., p. 65.
29. Ibid., p. 89.
30. Ibid., p. 87.

II.4 Augustus Waller

Description of the escape of white blood corpuscles through intact capillary walls (1846)

We turn now briefly to the observations of Augustus Waller (1814–1870) on the microcirculation.[1] In contrast to the work of Addison on the white corpuscles, which was commented on by investigators in England, Germany and France and made its way into textbooks of physiology and pathology, that of Waller on this subject remained unnoticed until Cohnheim's publication of 1867 brought it once again to light. Waller's description of the mode of escape of the white corpuscles failed even to gain the attention of his friend the microscopical anatomist Arthur Hill Hassall. This is all the more surprising in view of the fact that Hassall was well acquainted with Waller's technique for studying the

microcirculation in the tongue of the living frog.[2] We have seen also that it was Addison, not Waller, whose name appeared in the footnote to Cohnheim's paper of 1867, and this could hardly have been the case had either Virchow or Cohnheim been acquainted with Waller's observations. Whether Addison himself was familiar with Waller's description is doubtful. In any event his name nowhere appears in Addison's writings. Waller, on the contrary, was quite familiar with and sympathetic toward some of the claims of Addison.

It was an interest in a theory of muscle contraction that first brought Waller to his studies on the escape of white cells from the capillaries.[3] In the course of his observations on muscle contraction he introduced the use of the frog's tongue, finding at the same time that the flow of blood in the smallest vessels also could be advantageously studied in this way. Waller first attempted to study the microcirculation in the human prepuce, enlisting the aid of his teacher Alfred Donné in this endeavour. After a few trials they gave up, but not before Waller had told Donné of his frog preparation. Subsequently Donné mentioned the use of the frog's tongue in this connexion before the Société Philomathique in Paris (where Waller was studying at the time), without giving credit to his pupil. Waller then asserted his discoverer's rights, he says, at a meeting of the Société attended by Donné, who apparently did not dispute his claims. Nevertheless, when Donné described the use of the frog tongue preparation in his *Cours de microscopie* he said only that the initial idea had been given him by Waller, a foreign student who was attending his course.[4]

In Waller's procedure the frog is first swaddled in linen. Its tongue is then withdrawn, stretched, pinned out on a piece of cork and examined under the microscope. The long exposure to air and the abnormal positioning bring about an engorgement of the small vessels. Waller could see the appearances that had been familiar to two generations of observers before him: discs or globules passing in single file through the smallest vessels, oscillation and temporary

stagnation of the column of blood, occasional reversal of flow, and so on. With respect to the more recent observation that the white corpuscles became adherent to the walls of capillaries and small vessels generally Waller comments that the 'experiments of Mr. W. Addison of Malvern, have greatly contributed to show these important functions in inflammation', and that the presence of corpuscles adherent to the walls of vessels just above capillary size 'has been very aptly compared to so many pebbles or marbles over which a stream runs without disturbing them'.[5]

For the most part his first paper is concerned with the behaviour of muscle fibres undergoing contraction. A short appendix, dated 1846, contains the statement that some of his recent observations have enabled him to 'decide the much agitated question of the formation of pus, and its origin from the extravasation of the colourless or spherical corpuscles from the capillaries'. He had examined the mesentery of a toad that had been dead for about three hours. The mesenteric capillaries were found to be packed with corpuscles and discs lying at rest, but 'upon examining the membrane I observed corpuscles within the vessel, which disappeared from the spots where they had been previously detected, and after a few minutes were no longer to be found. The only traces of their former situation were curved indentations in the vessel, of the same size as the corpuscles, and a solution of continuity of the parietes of the vessel at those points.' He then examined the tongue of a live frog and found similar appearances. The already extravasated corpuscles lay near vessels with concave depression in their walls, and 'some of the corpuscles were protruding half out of the vessel'. In his opinion these findings established that (1) the corpuscles passed *de toute pièce* through the capillary wall, and (2) the restorative power of the blood immediately closed the aperture thus formed.[6]

Waller's second paper, 'Microscopical observations on the perforation of the capillaries by the corpuscles of the blood, and on the origin of mucus and pus-globules' appeared in the following issue of the *Philosophical Magazine*.[7]

He now remarks that the close visual resemblance between the colourless corpuscles in the circulating blood and those found in mucus and pus, including their content of granules and their like reaction to acetic acid, has attracted the attention of many observers and given rise to the supposition that the corpuscles of pus and mucus are extravasated white blood corpuscles. The further observation that white blood corpuscles accumulate in large numbers on the inner walls of irritated blood-vessels has strengthened the theory, principally championed in England by Mr. Addison. Other physiologists—here Waller mentions Müller, Autenreith and Donné—regard the perforation of capillary walls as a highly unlikely event and therefore reject the identity of the three kinds of corpuscles while admitting their close resemblance. His own observations have shown him the 'admirable manner in which nature has solved the apparent paradox, of eliminating, from a fluid circulating in closed tubes, certain particles floating in it, without causing any rupture or perforation in the tubes, or allowing the escape of the red particles, which are frequently the smaller of the two, or that of the fluid part of the blood itself'.[8]

But in order to see just how this takes place, Waller points out, it is necessary to keep the capillaries in view under the microscope for as much as two or three hours at a time. Where corpuscles had escaped from the bloodstream they could be observed singly or in small groups lying in indentations or cavities along the course of the greatly engorged capillary vessels. With persistent observation the actual manner of escape could be observed. First the corpuscles became adherent to the inner wall of the vessel and then 'that part of the tube in contact with the external side of the corpuscle gradually disappeared, and at nearly the same time might be seen the formation of a distinct line of demarcation between the inner segment of the corpuscle and the fluid parts of the blood in contact with it. Any slight agitation then was capable of disengaging the corpuscle from the vessel to which it was now external, and in its place a concave depression remained, which appeared sufficiently

protected by some membrane, as to oppose effectually the exit of the discs and the fluid parts of the blood.'[9] In the larger vessels the indentations were not to be found, but since corpuscles collected in abundance at various points external to their walls he thought it likely that 'the parieties of these also may be dissolved to allow the passage of these particles'.[10]

But precisely how did the corpuscles manage to pass through? Did it involve any active movements on their own part? Waller ascribes neither contractility nor mobility to the corpuscles. They are the moved rather than the movers. The movement took place even after the death of the animal and so could hardly be due to the 'influence of vitality'. He suggested that the corpuscles might give off a substance capable of dissolving the walls. Or perhaps the mere contact of corpuscle and wall had 'catalytic power'. Yet it was also true, he pointed out, that the white blood corpuscles could remain adherent to the inner surfaces of vascular walls for long spaces of time without altering them in the least.[11]

Waller promised to deal more fully with the formation of purulent matter on a future occasion, but if he ever did so and wrote on the subject his paper has not been uncovered. He continued to be an active investigator, but his interests, from the first, lay in fields other than inflammation. After Cohnheim's description of the passage of white cells through the intact walls of small blood-vessels was published in 1867 Waller's two papers were quickly brought to light and mentioned in an editorial of the *Medical Times and Gazette* dated 2 May 1868.[12]

Waller's report on the perforation of capillary walls by white blood corpuscles would seem to be ideal grist for the mill of the historian who wishes only to record the step-by-step accumulation of still accepted findings. Unlike Addison, Waller makes his observation and conveniently disappears from the scene immediately afterwards, without burdening the historian with hypotheses and theories. But Waller was not a pure observer and recorder in this instance.

He puts the question of the mode of transit of the corpuscles in the first place only because he is aware of the currently conflicting claims regarding their identity with the corpuscles of pus and mucus. He sees a limited number of white corpuscles perforate capillary walls in the abnormally irritated and positioned tongue of a cold-blooded amphibian, the frog. He then concludes (implicitly at least) that all pus and mucus corpuscles originate in this way in warm-blooded mammals, including man. The gap between evidence and conclusion, obvious in Waller's time to any critical scientist is likely to be concealed today from the historian by the dogmatic acceptance long since accorded to the claim in question and by the gradual restructuring of scientific knowledge so that other possibilities grow increasingly unlikely.[13]

Bibliography and Notes

1. Waller is best known for his demonstration that nerve fibres degenerate when separated from the parent cell bodies ('Wallerian' degeneration). *World Who's Who in Science* (op. cit.) credits him with this finding but says nothing of his work on white cell diapedesis. The *Biographisches Lexikon* (op. cit.) says of his two papers in the *Philosophical Magazine*: 'Hier zeigt sich Waller als Vorgaenger Cohnheims in der Entzuendungslehre.' Garrison and Morton's *Bibliography* (op. cit.) does not list his papers on diapedesis. Garrison's *Introduction to the History of Medicine* (op. cit.) offers a thorough discussion of his work in neuropathology but does not mention his description of diapedesis.
2. On p. 70 of Hassall's *Microscopic Anatomy* (op. cit., 1849) Hassall refers to Waller as a friend and neighbour who had acquainted him with a useful technique for studying the circulation in the frog's tongue under the microscope. But since Hassall states on p. 129 (in reference to Addison) that 'the direct passage of the white corpuscles of the blood appears never to have been clearly witnessed' it would seem that he was unacquainted with Waller's observations. Or perhaps Waller had by that time privately disavowed them?
3. Augustus Waller, 'Microscopic examination of some of the principal tissues of the animal frame, as observed in the tongue of the living frog, toad, etc.', *Phil. Mag.*, 3rd series, 1846, **29**, 271–87.
4. Ibid., pp. 272–73.
5. Ibid., pp. 285–87.
6. Ibid., pp. 285–87.

7. Augustus Waller, *Phil. Mag.*, 3rd series, 1846, **29**, 397–405.
8. Ibid., pp. 397–98.
9. Ibid., p. 399.
10. Ibid., p. 400.
11. Ibid., p. 402.
12. Editorial, *Med. Times Gaz.*, 1868, **53**, 473–74. The writer refers to Cohnheim's 'rediscovery of a lost fact'. While accepting the fact he states that the future will show 'whether this is the only or even the most common mode in which the process takes place'. In Uhle and Wagner's *Handbuch der allgemeinen Pathologie, herausgegeben von Dr. Ernst Wagner* (7th ed., Leipzig, 1876) a note on p. 341 states that Doellinger, Müller, Koch, Hassall, Kaltenbrunner, Zimmermann and Addison observed the escape of white cells from vessels and explained the origin of pus corpuscles in this way, while Waller was the first to depict the process in an accurate fashion. Wagner's statement is incorrect on several points. Neither Doellinger, Koch nor Kaltenbrunner—the latter in his *Experimenta circa statum sanguinis et vasorum in inflammatione* (Munich, 1826)—described the process of migration or clearly distinguished red from white corpuscles. Müller (*Handbuch*, op. cit., 1st ed., 1833, p. 243) states flatly that the corpuscles of pus 'koennen nicht aus den Blutkoerperchen ihre Entstehung nehmen'. Hassall (op. cit.) first accepted and then rejected Addison's claims. Those of Zimmermann rested on hypothesis rather than observation.
13. These remarks apply to the polymorphonuclear leucocyte. Only a vanishingly small number of observers (e.g. Busse-Grawitz, 'Molekularpathologie und Cohnheimsche Leukocytenlehre', *Zentralbl. allg. Path. path. Anat.*, 1957, **96**, 376) now claim that cells of this kind originate extravascularly at sites of inflammation. As for the question of whether certain other cells of inflammatory exudates are necessarily migrants, the dispute continues.

II.5 Pyaemia, Leucocytosis and Leukaemia at Mid-century

We pause now in our examination of Addison's writings to follow some interesting developments that took place in the eighteen forties with respect to the number of colourless blood corpuscles present in the circulating blood under normal and abnormal conditions. We shall see that these

developments are related to one aspect of Addison's work, since he played a small role in the discernment of what was later to be known as inflammatory leucocytosis, i.e. the increase in total number of circulating colourless corpuscles associated with inflammation somewhere in the body.

The term *pyohémie* (pyohaemia or, more commonly, pyaemia) was introduced in 1828 by Pierre Piorry as a designation for a disease or clinical condition long familiar to physicians and surgeons and thought by many to be due to the absorption of pus from foci of suppuration into the circulating blood.[1] The older writers on the subject, those whose work was done before the more general use of the microscope, had not been concerned with the pus corpuscles themselves. But Piorry was, and in his opinion pus corpuscles could pass freely from abscesses and other zones of suppuration into the bloodstream. From the bloodstream they could once again pass back into the tissues and so create secondary abscesses. As the blastema theory came to predominance, together with the increasing evidence that the capillaries were provided with complete membraneous walls (impermeable to bodies as large as blood corpuscles, although permitting the passage of the fluid or finely granular proteinaceous blastema or plasma of the blood) the idea lost its attractiveness for the more advanced workers in physiology and pathology. Addison himself did not deal specifically with pyaemia, but the older idea is obviously consonant with his own views. Zimmermann agreed with Piorry and we have already seen how he was taken to task by Virchow for doing so.[2] Virchow was at the time thoroughly committed to the blastema theory, and he held also that osmotic interchange took place through membraneous walls of capillaries forbidding the passage of cells in either direction.[3]

Like almost all investigators Virchow admitted the resemblance between certain (not all) of the corpuscles found in pus and those present in the circulating blood. But in his opinion the blood was, like all fluids containing cells or corpuscles, a *tissue*, and one undergoing constant growth, development and change. It was therefore a mistake to

group transient cell forms together on the basis of their mere temporary resemblance. It was also a mistake to characterize the form taken by a given cell at some stage of its development as the type of, say, *the* pus cell, *the* colourless corpuscle of the blood, *the* cancer cell and so on.[4] A transitory form assumed by a developing cell could not legitimately be used as the type with which to classify other cells. As for white blood corpuscles and pus corpuscles both were, in Virchow's opinion, relatively embryonal cells newly sprung from the blastema. Virchow's reluctance to accept the identity of pus corpuscles and white blood corpuscles on the basis of what he considered a mere resemblance between some of the forms they assumed in the course of their development was to bear fruit in connexion with his description and designation of a new and distinct disease, unrelated to pyaemia and characterized among other things by the presence of enormous numbers of white blood cells in the circulating blood.[5]

The term 'leucocytosis' was later applied by Virchow to the more or less transitory increases in the total number of circulating colourless corpuscles occurring in both health and disease. He rejected the concept of pyaemia entirely, except in those rare instances where pus could be known to have made its way into the bloodstream from a focus of suppuration via damaged or destroyed vascular walls, usually those of medium size. For investigators who both identified pus corpuscles and colourless corpuscles and allowed for the passage of these corpuscles through more or less intact vascular walls, the older concept of pyaemia remained valid. The situation was further complicated around 1840 by the incomplete recognition accorded to colourless corpuscles as normal constituents of human blood. For example, in 1838 Gulliver claimed that he had detected 'pus in the blood in almost every instance in which there was either extensive suppuration, or great inflammatory swelling without a visible deposition of pus in any of the textures of the body'. His procedure was to dissolve the corpuscles in drawn blood by adding water before coagulation occurred. The pus cor-

puscles were unaffected and they sank to the bottom of the vessels, where they could then be detected with the microscope. For Gulliver, at this time, the 'corpuscles' of the blood are the red corpuscles alone, hence he gives the name 'pus' corpuscle to those demonstrated by his procedure, recognizing their similarity to the corpuscles of pus. But he traces the origin of pus corpuscles themselves to the blood corpuscles, for, 'since the microscopic investigations of Mr. Hunter, Sir Everard Home and Mr. Bauer, the opinion has often been expressed that the globules of pus are nothing, but those of blood modified by the inflammatory process'. It may be asked, says Gulliver, 'if, on a suppurating surface, the pus globules, considerably larger than those of the blood, escape from the capillaries, how comes it that the latter particles do not escape as well'? He suggests in answer that the breaches of continuity in the vascular walls are closed by coagulation of the fluid elements of the blood within.[6] We may note that Gulliver's report does not bear on an increase of white cells in the blood as such, since he does not recognize their presence in the blood of normal persons. The only pus corpuscles to be found in blood have been absorbed from foci of suppuration in the tissues, so he believes.

A slightly different view was expressed by Henry Ancell in 1840 in a series of lectures on the physiology and pathology of the blood. Ancell notes that Gulliver and others have detected pus globules in the circulating blood in patients with febrile, inflammatory or suppurative disease but considers resorption of the globules from the tissues a highly unlikely explanation of their presence in the blood. It is much more probable, he writes, 'that they are formed in inflamed blood within the vessels . . . it is not likely they are received without the vessels'.[7] Ancell is aware that 'Magendie and others describe large white globules as normal constituents of the blood', although he finds that these globules more nearly resemble the globules of pus and mucus than Magendie's description of them suggests. Although few in number they are constantly present in the blood of all animals, including man.[8] Finally, Ancell has

seen 'several instances of suppuration in which the white globules of the blood were much more numerous than those described as occurring constantly during health; and they had the same form, colour, magnitude and appearance, as the true pus-globules. . .'. His report is only roughly quantitative, of course, but it might reasonably be held to constitute a description of what was later to be called 'leucocytosis'.[9] We know that Addison on two occasions, in 1842 and 1843, had described an increase in the number of white corpuscles in blood drawn from the skin at or near sites of inflammation, and that chiefly on this basis he was later accorded priority in the description of leucocytosis. The other support for his claim might rest on his showing that the buffy coat of 'inflammatory' blood was rich in white cells. Addison was actually given some credit at the time in this connexion. The writer of an article in the *British and Foreign Medical Review* of July 1844 points out that our knowledge of the increased proportion of colourless corpuscles in inflammatory blood and their local accumulation in the vessels of inflamed parts is the result of observations made independently by Gendrin, Gulliver, Addison and Williams.[10] Gulliver had earned his place here by contributing, about two years before, an article in which he noted that in inflammatory affections the pus-like (as he now calls them) globules in the blood were much more numerous than in a state of health.[11]

In connexion with the various bits of evidence in favour of overall increases in the number of colourless corpuscles in the circulating blood Wharton Jones had some pertinent comments to make in 1844. The evidence, he said, was as follows: (1) colourless corpuscles were known to accumulate on the walls of vessels in inflamed parts; (2) large numbers of colourless corpuscles were to be found in the *liquor sanguinis* rising to the top of drawn blood contributing to the formation of a buffy coat where inflammatory disease was present; (3) Mr. Gulliver's observations of 1838 had been adduced by Dr. Carpenter as evidence for a concomitant increase in white corpuscles when the fibrin content of the

blood rose in connexion with inflammatory disease. But, said Wharton Jones, the accumulation of colourless corpuscles in the vessels of an inflamed part is no more evidence of an overall increase in their number in the circulating blood than the 'occurrence of a crowd in the street before one's window can be reckoned an indication that the number of inhabitants of London is amazingly increased'.[12] In an earlier review he had already pointed out that while the number of colourless corpuscles might well be increased in buffy blood the increase was probably more apparent than real, being due largely to the more rapid settling out of red corpuscles. His own examination of freshly drawn inflammatory blood, before it became buffed, had not revealed any very marked increase in colourless corpuscles over that seen in health. As for Gulliver he had simply found pus corpuscles in inflamed blood, being at that time 'naturally' unaware of the presence of such corpuscles in healthy blood. Had he used his procedure on blood drawn from healthy persons, said Wharton Jones, he would have detected the so-called pus globules there as well.[13]

We come now to those instances of enormous and persistent increase in the number of circulating white blood cells that characterize the disease called 'leukaemia' by Virchow and 'leucocythaemia' by Bennett. Bennett's initial report on the subject, combined with one by David Craigie, appeared in the October 1845 issue of the *Edinburgh Medical and Surgical Journal*.[14] Craigie's patient, first seen in 1841, had succumbed to a peculiar ailment that ran its course in about twelve months. Toward the end, fever was a prominent symptom. A post-mortem examination showed the liver and spleen to be immensely enlarged and the blood vessels to be filled with clots that 'contained lymph or purulent matter'. Yet there was no evidence of inflammation or abscess anywhere in the body. Craigie suggested that the spleen was inflamed in some peculiar way and was thus discharging purulent matter into the bloodstream, an abscess not being evident because of the peculiar structure of the organ. It was the presence of purulent

matter in the blood that had caused the observed symptoms of inflammatory and febrile disorder, in his opinion. About three years later another patient with an enlarged spleen and rather similar symptoms came under Craigie's care. Here too the disease ran a fatal course. The post-mortem findings on this patient, he says, including a microscopic study (not carried out on the first patient), will be reported by Bennett. The promised report begins with Bennett's remark that many authors have previously claimed to have found purulent matter in the blood independent of local inflammation or abscess, but none has proved that the 'purulent-looking matter was really pus'. In the case that has now come to his attention the blood was found to contain numerous granular corpuscles of the size and appearance of pus corpuscles. In addition, they showed the same reaction to water and acetic acid.[15] Since there was no evidence of phlebitis, abscess or inflammatory process anywhere in the body the problem was, How to explain the enormous number of pus corpuscles in the blood? And in Bennett's opinion they *were* pus corpuscles. 'The only corpuscles with which they can be confounded are the colourless corpuscles of the blood itself', he writes, and 'with regard to the colourless corpuscles of the blood we know of no instance where they existed in the amount, or ever presented the appearance described'. Bennett attempted to explain the 'production of pus independent of inflammation' as follows: The corpuscles of pus arise in a blastema consisting of *liquor sanguinis* that has exuded through the walls of blood-vessels. If that blastema were to be separated from the red corpuscles *within* the blood-vessels there would be 'no reason why these pus cells should not be formed in it'.[16] It is important to note here that although Bennett designated the condition 'suppuration of the blood', he thought that the suppuration had arisen independently of inflammation. The pus corpuscles in the blood had not been resorbed (the old explanation for pyaemia given by those who regarded the small blood-vessels as permeable to corpuscles); they had been formed *within* the bloodstream.[17] Bennett might have called

(although he did not) his patient's disease a kind of 'internalized' pyaemia. How did Bennett manage, to his own satisfaction, to distinguish between pus corpuscles and the colourless corpuscles normally present in the blood? And why did he not simply assume that some causal factor or other had brought about a great increase in the number of colourless corpuscles in the blood? Had he done so and clearly stated that his patient's disease had nothing to do with suppuration the dispute with Virchow over priority rights would never have occurred. Clearly Bennett could not in fact distinguish pus corpuscles from colourless blood corpuscles. But he was unable to free his mind from the notion that the peculiar disease in these two patients was somehow related to 'suppuration of the blood'.

Virchow's first paper was entitled 'White Blood'. It appeared about six weeks after Craigie and Bennett's report.[18] Virchow first noted that in 1760 von Haller had described a patient whose blood resembled milk, mucus or pus.[19] In his own case, a man whose disease terminated fatally in a little more than a year, the spleen was tremendously enlarged, the liver unchanged, and the blood so packed with white cells that the normal ratio in favour of the red cells was reversed. The white cells displayed round, horseshoe-shaped or cloverleaf-like nuclei. Virchow then pointed to a possible counterpart of his patient's disease in a case report emanating from Vienna, published in 1845. In that instance the diagnosis of pyaemia had been made. But, says Virchow, in pyaemia the essential feature is liquefaction and breakdown of blood constituents, together with a tendency toward purulent metamorphosis of exudates. As for the question of whether the cells in question were pus corpuscles or white blood cells, Virchow regarded it as unanswerable on the basis of appearance alone. In his second paper, published somewhat less than a year later, Virchow reviewed a number of reported cases similar to his own (including those of Bennett and Craigie) and put them into the new disease category that he was attempting to establish.[20] In one of these cases, incidentally, the increased number of

colourless corpuscles became evident while the patient was still alive.[21] Virchow did not share Bennett's opinion that the disease was a pyaemia of sorts due to a peculiar fermentative activity occurring within the blood. He did agree with Bennett that the condition was a 'disease of the blood'.[22] Near the close of this paper Virchow writes, 'I hereby claim a place in pathology for the colourless blood corpuscle'. He rejects a microscopical diagnosis of pyaemia as illusory, on the ground that pus corpuscles are never resorbed from foci of suppuration to appear within the bloodstream, as the older writers supposed. Pus corpuscles and colourless blood corpuscles look alike but are different by reason of origin.[23] Virchow defended and amplified his views in two further articles, both published in 1847. In the second of these he used the Greek equivalent of 'white blood', leukaemia, as a name for the new disease.[24]

Nothing more on the subject by Bennett was published until 1851, when a series of papers began to appear in the *Monthly Medical Journal*.[25] The first of these bore the title, 'On leucocythaemia, or blood containing an unusual number of colourless corpuscles'. It is the only one of the group in which the name of Virchow appears and then only so that Bennett can reject Virchow's designation of the disease in question as 'leukaemia' and assert his own priority in its discovery.[26] The blood was not really white in the disease. It did contain many white blood cells, hence his was the more suitable name. Bennett's series of papers give the findings on thirty-five patients in whom the diagnosis of leucocythaemia had been made during life or after death, the youngest being a girl of nine years, the oldest a woman of sixty-nine. Throughout he now refers to the cells in the blood as colourless corpuscles rather than pus corpuscles, although he does once mention their resemblance to the latter. At the conclusion of the case reports Bennett states that he will endeavour to show, in a subsequent memoir, that the colourless blood corpuscles are derived from the lymphatic glandular system.[27]

The promised memoir appeared in the following year.

Bennett rested his claim on the following evidence: (1) cells or corpuscles of the lymphatic glandular system resemble each other and the colourless cells of the blood; (2) the glands of this system lack excretory ducts, hence whatever they produce must pass into the bloodstream, and (3) the blood of the splenic vein (the spleen being part of the system, according to Bennett) had been shown to contain more white corpuscles than blood elsewhere in the body. As for the mode of production of the corpuscles, Bennett thought that they might be either 'thrown off, in the form of epithelium, from the membrane which surrounds them' or take their origin from 'an organic fluid, by the production of molecules, the successive development and aggregation of which constitute the higher formations'. He thought the latter alternative more in keeping with the 'known facts'.[28] Finally, Bennett closed his presentation of leucocythaemia with an additional paper in which he dealt with the problem of the relation between the new disease and pyaemia. He remarks on the resemblance between pus corpuscles and the colourless cells of the blood, adding that in the first instance of leucocythaemia that came to his attention he 'could not resist the conclusion that the blood was crowded with pus cells'.[29] Again the work of Virchow was pointedly overlooked. For details of the controversy between the two men and their supporters the reader is referred to the notes.[30]

The names of Addison and Williams also make a brief appearance here. Bennett says that they have wrongly taken the 'occasional and accidental accumulation of the colourless corpuscles within some of the smaller vessels' to be important or even essential in the inflammatory process. But their theory of inflammation, 'which never reposed on accurate observation even in frogs', has received its *coup de grâce* from his discovery of leucocythaemia. For in this disease 'the colourless corpuscles *are* increased in number in the smallest vessels, and yet, instead of a universal inflammation, persons live in that condition for months and years'.[31]

1. Peter Murray Braidwood, *On Pyaemia, or Suppurative Fever*, London, 1868.
2. Cf. Introduction, note 1. Addison never mentions Zimmermann, although he may well have been acquainted with his writings. The *Medico-Chirurgical Review*, N.S., 1844, 41, 145–46, carries a résumé of an article by Zimmermann that had been published in Germany the year before. In Zimmermann's opinion pus corpuscles, possibly by virtue of a lytic effect, were capable of passing through intact capillary walls (cf. Waller's related notion).
3. In 1847 Virchow gave the laws of 'physiological and pathological formation' as follows: (1) All organization takes place through the differentiation of a formless substance, the blastema; (2) All blastema passes out of the blood-vessels as a fluid exudate; (3) All organization begins with cell formation (this he calls Müller's law); (4) Beyond a certain point in their development nothing more can come from cells; they are transitory formations. As for the precise way in which new cells originated Virchow found it difficult to decide whether they were formed more commonly in an extracellular blastema or within pre-existing cells in an intracellular blastema ('Ueber die Reform der pathologischen und therapeutischen Anschauungen durch die mikroskopischen Untersuchungen', *Arch. path. Anat. Physiol. wiss. Med.*, 1847, 1, 205–55, cf. p. 218).
4. Virchow, *Ueber die Reform* . . ., op. cit., pp. 213–15 calls this 'ontologizing'. First a granulated cell with three to five nuclei was proclaimed *the* pus cell; later it was regarded as the cell of *pus bonum et laudabile* only. The mistake, according to Virchow, was the study of *states* instead of *processes* in what was in actuality a fluid tissue undergoing developmental changes . . . 'pus, a tissue of transitory significance undergoing rapid development, consists of cells and a protein-like intercellular substance, and arises from a fibrinous blastema that has accumulated under abnormal conditions' (op. cit., p. 240). J. F. Meckel, wrote Virchow, had extended the concept of a tissue to cover fluids containing formed constituents; Reichert and Henle had specifically included blood among these fluids.
5. Erwin Ackerknecht refers to the belief that white cells are unable to penetrate vascular walls as a 'pet error of Virchow, corrected by his pupil Cohnheim in 1867 . . . which in this case helped him to find the truth', i.e. that leukaemia was a distinct disease entity (*Rudolf Virchow: Doctor, Statesman, Anthropologist*, Madison, 1953, p. 65). But in fact Virchow merely shared the advanced scientific opinion of his day. The phrase 'pet error' might better be applied to T. Wharton Jones, who in 1891, the year of his death, still spoke of 'the unsatisfactory characters of the observations of Cohnheim, his predecessors and followers on

the subject' of the migration of white cells (*Report on the State of the Blood and the Blood-vessels in Inflammation*, London, 1891, cf. note on p. 35).

6. George Gulliver, 'Researches on suppuration', *Phil. Mag.*, 3rd series, 1838, **13**, 193–202.
7. Henry Ancell, 'Course of lectures on the physiology and pathology of the blood, etc.', *Lancet*, 15 August 1840, 739–49.
8. Ibid., *Lancet*, 22 August 1840, pp. 722–81. Mandl, according to Ancell, 'states confidently that they are coagulated fibrin, and identical with the pus and mucous globule'.
9. Ibid., p. 777. The comments of Julius Vogel in 1854 are of interest in connexion with attempts then made to determine the number of white corpuscles per unit volume of blood. Vogel suggests two methods, (1) determining the ratio of white cells to red cells in a drop of blood, (2) allowing blood that has been defibrinated by whipping to settle in a high narrow vessel. The width of the upper layer, consisting of white cells only, gives a good measure of their amount. (The modern haematologist adds an anti-coagulant before spinning the blood down in a narrow tube; the upper layer is the modern 'buffy coat'.) Vogel states that a procedure for the precise enumeration of white blood cells is being developed (Julius Vogel, in *Handbuch der speciellen Therapie*, ed. by Rudolf Virchow, 6 vols., vol. 1, p. 392, Erlangen, 1854).
10. Unsigned article in *Brit. for. med. Rev.*, 1844, **18**, 91–114.
11. George Gulliver, 'On the pus-like globules of the blood', *Brit. for. med. Rev.*, 1843, **15**, 234. Gulliver claims that the pus-like globules are larger, more irregular in size and shape, and more opaque than the colourless globules in the blood of healthy animals.
12. T. Wharton Jones, 'Report on the changes in the blood in inflammation, and on the nature of the healing process', *Brit. for. med. Rev.*, 1844, **18**, 225–80, Wharton Jones notes that Gendrin's authority has been called upon to support the alleged increase in colourless corpuscles, but that he himself can find no such statement in Gendrin's *Histoire des inflammations* and doubts that at the time of its publication in 1828 Gendrin knew of the existence of colourless corpuscles in the human blood under normal conditions.
13. Ibid., pp. 259–60. Wharton Jones refers here to his paper in *Brit. for. med. Rev.*, 1842 (op. cit.). Wrong though he proved to be, his analysis is correct on all points. As for his failure to find marked increases in freshly drawn blood we must remember that a doubling of the usual number of leucocytes in the circulating blood would merely change the ratio of white cells to red cells from, say, 1/500 to 2/500; in the absence of a precise method of counting this would indeed not be a very marked increase.
14. David Craigie, 'Case of disease of the spleen, in which death took place in consequence of the presence of purulent matter in the blood', *Edinb.*

med. surg. J., 1845, **64**, 400–13; John Hughes Bennett, 'Case of hypertrophy of the spleen and liver, in which death took place from suppuration of the blood', ibid., pp. 413–23. (The two reports appear as Case 1 and Case 2 of Art. VIII.)

15. Bennett, op. cit., p. 418, gives the size range as 1/80th to 1/120th of a millimetre. The nucleus was usually single, measuring about 1/200th millimetre in diameter. Some of the nuclei, said Bennett, had two or three parts similar to those seen in cells of laudable pus. In Craigie's case the spleen weighed 7 lb. 3 oz., the liver 6 lb. 3 oz., and enlargement of the lymph nodes was not noted. In Bennett's case the spleen weighed 7 lb. 12 oz., the liver 10 lb. 12 oz. and the lymph glands were greatly enlarged.
16. Bennett, op. cit., p. 422. He suggests that a transformation of the whole mass of the blood has taken place, analogous to fermentation or 'zymosis'.
17. Bennett, op. cit., p. 421, rejected Piorry's concept of 'haematitis' (inflammation of the blood) but if such a lesion could be imagined, he wrote, his patient would represent a case in point. But it makes no sense to speak of inflammation in the absence of an exudation from the blood-vessels, says Bennett.
18. Rudolf Virchow, *Weisses Blut*, Froriep's Neue Notizen, Nr. 780, November 1845, reprinted in Virchow's *Gesammelte Abhandlungen zur wissenschaftlichen Medizin*, Frankfurt a.M., 1856, pp. 149–54.
19. Ibid., p. 149.
20. Ibid., pp. 154–73. The paper originally appeared in the *Medicinische Zeitung des Vereins für Heilkunde in Preussen*, Nr. 34–36, August–September 1846.
21. Henry W. Fuller, 'Particulars of a case in which enormous enlargement of the spleen and liver, together with dilatation of all the blood-vessels of the body, were found coincident with a peculiarly altered condition of the blood'; in the abstracts of the Royal Medical and Chirurgical Society, *Lancet*, 11 July 1846, 43–44. Fuller's patient had an enlarged and indurated spleen of the kind 'so frequently met with in malarial districts'. The disease ran a course of about nine months. At post-mortem examination an enormous liver and spleen were found, and the blood throughout was 'grumous and grey'. The writer of the abstract states that while the patient was still alive 'the author had three times examined the blood under the microscope . . . on each instance he found, in addition to the natural blood corpuscles, a very large proportion of abnormal, granular, colourless globules, which he proceeds more particularly to describe'. He adds that Fuller 'does not refer the local enlargement to inflammatory action, or to obstruction to the circulation, caused by the presence of these granular globules, but looks upon them, together with the dilatation of the blood-vessels, the altered condition of the blood itself, as simple evidences of perverted nutrition, in themselves the effect of one and the same cause'.

22. Virchow, *Gesammelte Abhandlungen*, op. cit., p. 172.
23. Virchow's opinion is as follows: 'The pus cell arises in the plasma exudate just as the cell of the chyle in the chyle, and probably also the colourless blood cell in the chyle or blood plasma. The law of development for the pus cell and the colourless cell of the blood is the same; both are relatively embryonal cells that are only distinguished from each other in that from the latter connective tissue *may* finally arise, from the former red corpuscles' (*Gesammelte Abhandlungen*, op. cit., p. 168).
24. *Medicinische Zeitung*, Nr. 3, 4, January 1847, reprinted in *Gesammelte Abhandlungen*, op. cit., pp. 173–79; also 'Zur pathologischen Physiologie des Blutes' in *Arch. path. Anat. Physiol. klin. Med.*, **1**, 547–83, esp. p. 563. In the article in the *Medicinische Zeitung* Virchow discusses various conditions associated with an increase in the number of colourless corpuscles in the blood. He credits Nasse with the first accurate description of colourless corpuscles as well as with the first discussion of increases in their number in the circulating blood (citing Nasse's *Untersuchungen zur Physiologie und Pathologie*, 1839, II, S. 150). Nasse, says Virchow, found that their number was increased in pregnancy and inflammatory conditions. Donné regarded a rise in the number of colourless corpuscles in the blood as the consequence of a failure in their normal transformation into red corpuscles and denied that the increase should be interpreted as the passage of pus corpuscles into the blood. In none of the instances mentioned by Virchow were quantitative techniques employed; the number of white cells is simply said to be 'increased'. Summing up, Virchow found that increases in the number of white blood corpuscles in the circulating blood occurred (1) after great blood loss, as shown by Nasse, Remak and Henle, (2) in chronic, exhausting diseases, as shown by Gulliver, (3) in acute inflammatory diseases, especially pneumonia and puerperal fever, and (4) in pregnancy. (He did not at this time use the term 'leukocytosis'.) Bouchut's report of 1844 of an increased number of white globules found at post-mortem examination in the blood of a woman with puerperal fever comes closer to quantitation than any mentioned by Virchow. Bouchut observed that a drop of blood taken from a healthy person and examined under the microscope contained 10 to 20 white globules, whereas that of his patient contained 130 to 150 under the same conditions. He concluded that the additional white globules were *not* those ordinarily seen in healthy blood; they were pus globules ('Études sur la fièvre puerpérale; par le docteur Bouchut', *Gaz. méd. Paris*, series 2 w, 1844, **12**, 85–90).
25. John Hughes Bennett, 'On leucocythaemia, or blood containing an unusual number of colourless corpuscles', *Mthly J. med. Sci.*, 1851, **12**, 17–38. 'On leucocythaemia or white cell blood', ibid., **12**, 313–26, 1851; 'On leucocythaemia or white cell blood', ibid., **13**, 315–35, 1851. Bennett's collected papers on this subject were published in book form: *Leucocythaemia, or White Cell Blood*, Edinburgh, 1852.

26. Bennett, *Mthly J. med. Sci.*, op. cit., pp. 17, 18. In reply Virchow stated that 'leucocythaemia' was itself an unsuitable term because white cells were normally present in the blood. Had Bennett used the term 'poly-leucocythaemia', said Virchow, he would at least have made it plain that there was an increase above the normal number. But this term, too, would not have been preferable to 'leukaemia', for the number of white cells in the blood was known to increase under several physiological and pathological circumstances (Virchow, *Gesammelte Abhandlungen*, op. cit., p. 191). It appears that Virchow had not yet coined the term 'leucocytosis'. Two years later, in the 1st ed. of his *Die Cellularpathologie* (Berlin, 1858), he uses 'leucocytosis' without comment as to its origin. Henry Allen Skinner, in *The Origin of Medical Terms* (Baltimore, 1949) p. 212 states that Virchow first used this term in 1865. Ackerknecht, *Rudolf Virchow: Doctor, Statesman, Anthropologist*, op. cit., p. 66, credits Virchow with the introduction of the term, but gives no citation.
27. Bennett, op. cit., p. 335. According to Bennett the lymphatic glandular system includes the 'spleen, supra-renal capsules, thyroid body, thymus (pituitary, pineal?) and lymphatic glands'.
28. John Hughes Bennett, 'On the function of the spleen and other lymphatic glands as secretors of the blood', *Mthly J. med. Sci.*, 1852, **14**, 200–13. The article contains some excellent drawings of the colourless cells seen in leucocythemic blood arranged in order of their presumed states of development. The nucleus is first spherical, then successively staff-shaped, horseshoe-shaped, and divided into three apparently separate granules. Bennett concurs with Wharton Jones, he says, in believing that red blood corpuscles are free nuclei, i.e. nuclei that have been released into the circulation at the nuclear stages of growth (not nuclei that have been released from colourless cells). He also gives drawings of cells in the spleen that contain bodies resembling red blood globules or 'coloured nuclei' and remarks that they have been interpreted by some as new blood corpuscles forming within mother cells, by others, including Kölliker, as old corpuscles undergoing dissolution.
29. 'On leucocythaemia or white cell blood', ibid., 1852, **14**, 331–45. Cf. p. 338.
30. The long and bitter priority dispute between Virchow and Bennett over the discovery of leukaemia was due partly to the uncertain position occupied by the colourless cells of the blood at the time, partly to lack of agreement as to what constituted discovery in such instances, and partly to the ease with which controversialists are apt to exchange what they now mean with what they once said. Virchow was no doubt already annoyed by the fact that Bennett (in the series of publications beginning in 1851) had passed over his own name but had at the same time appropriated his view that the cells in question were *not* pus corpuscles. When he read in a medical journal published in New York that he and Bennett had simultaneously described 'leucocythaemia' he must have decided that the time

had come to set the record straight. He thereupon issued his priority claim. In doing so he mentioned the habit of appropriating other men's intellectual products said to be characteristic of the Scots ('Nachschrift' to his 'Zur pathologischen Physiologie des Bluts', *Arch. path. Anat. Physiol. klin. Med.*, 1854, **5**, 43–128). At about the same time appeared, under Virchow's editorship, the first volume of the *Handbuch der speciellen Pathologie und Therapie* (Erlangen, 1854). The section on diseases of the blood was written by Julius Vogel, who gives the rival designations 'leukaemia' and 'leucocythaemia', describes the work of Bennett and Virchow, and awards Virchow the merit of having first described the new disease. Subsequently an unsigned review of the *Handbuch*, in all probability written by Bennett called Virchow's claim to priority 'coarse and unmannerly' and hinted at plagiarism (*Mthly J. med. Sci.*, 1854, **17**, 546–49). Virchow's colleague at Würzburg, Rudolf Kölliker, responded to the review with a long letter analysing the rival claims. The letter, together with a reply by Bennett were printed in full in the *Mthly J. med. Sci.*, 1854, **19**, 374–81. Kölliker's version of the events is: (1) Craigie and Bennett, in October 1845, publish the first microscopical examination of the blood in leukaemia, but do so 'on the assumption of purulent formation in the blood'; (2) Virchow, in November 1845 describes a new disease, leukaemia, and calls it a blood disease unrelated to pyaemia; (3) Virchow, in 1847, separates splenic and lymphatic forms of the new disease; (4) Bennett, in 1851, 'gives up his former views of leukaemia as a suppuration, adopting the explanation of Virchow, without mentioning his name'. Bennett's counterversion of the same events is: (1) Bennett, in October 1845, describes a 'new morbid condition of the blood, consisting of multitudes of corpuscles, resembling those of pus'; (2) in 1845 'confirmation of the preceding facts' by Virchow; (3) description of the lymphatic form of the new disease by Virchow in 1847; (4) Bennett's 'systematic review of the whole subject in 1851'. The distinction between pus corpuscles and colourless corpuscles of the blood on which Kölliker and Virchow laid so much weight had, said Bennett, no importance in view of the fact that the two kinds of cell were indistinguishable on morphological grounds. The pus corpuscles originated from without the vascular system, the white cells from within. Relations between Virchow and Bennett had been further worsened by a reference to the 'snarling writings of Virchow' (in *Mthly J. med. Sci.*, 1853, **17**, 447–48) that Virchow by a bit of detective work traced to Bennett himself ('Ein Sendschreiben an die Redaction des Monthly Journal of Medical Science zu Edinburgh', *Arch. path. Anat. Physiol. klin. Med.*, 1854, **6**, 426–32).

A balanced view of the controversy came in 1869 from the pen of a writer in France. It is all the more praiseworthy in that although its author pointed out that Donné had in certain respects anticipated both Virchow and Bennett he made no chauvinistic plea in favour of his countryman.

He noted that in 1844 Donné had (on p. 132 of his *Cours de microscopie*) described a patient with an enlarged spleen and an increased number of white cells in the blood. Donné had suggested that the condition represented a 'kind of arrest of development of the blood'. Nevertheless he could not be credited with the discovery of leukaemia because he had failed to create the picture of a full-fledged disease entity from his chance observation. With respect to the controversy between Virchow and Bennett the same considerations held. Bennett, it was true, had recorded his case before Virchow, but to establish a medical discovery 'it does not suffice to record only the chance encounter of a fact, even the exact description of lesions or clinical data; it is necessary above all to consider the interpretation which has been given them, the exact relation established between anatomical lesions and symptoms, and above all the clearly expressed conception of a new disease, different from those known heretofore, in a word the notion of a disease-entity' (E. Isambert, art. 'Leucocythémie', *Dictionnaire encyclopédique des Sciences médicales*, 2nd ed., Paris, 1869, cf. pp. 356–64).

31. Bennett, *Mthly J. med. Sci.*, 1852, **14**, 338.

II.6 Addison's *Law of the Morphology and Metamorphosis of Textures* (1847) and his book *On Healthy and Diseased Structure* (1849)

Nothing of moment seems to have come from Addison's pen during the two years that followed the publication of the second half of the essay on nutrition and inflammation in 1845.[1] But during this time he was clearly busy acquiring some new ideas, as we learn from a series of eleven papers on the morphology and metamorphosis of tissues contributed to the *Provincial Medical and Surgical Journal* from January to September of 1847.[2] Two years later appeared his most ambitious work, a book entitled *On Healthy and Diseased Structure and the True Principles of Treatment for the Cure of Disease, Especially Consumption and Scrofula; Founded on Microscopical Analysis*.[3] Much of its content had already been set forth in the series of eleven papers. But they dealt with physiology and pathology alone, while the first part of

the book included a brief section on psychological medicine as well, and the second a detailed discussion of the semeiology, aetiology and therapy of tuberculous disease, i.e. of consumption and scrofula. The book and the series of papers will be treated as a unit in this section and dealt with insofar as they bear on our topic. Some additional comments will be found in the notes and in Appendix A.

The introduction to the book contains the new ideas that Addison has acquired in relation to the cell theory in plants and animals. He now regards Lorenz Oken (1779–1851) as the herald of cell theory and the first to announce that plants and animals are composed entirely of 'cell-organisms', those primary forms of life from which 'all larger and more compound structures were originally evolved'.[4] Addison has become acquainted with an idea new to him, that of 'metamorphosis', and he intends to apply it to his own theories of inflammation and nutrition.[5] Normal metamorphosis is matched on the side of pathology by two variants, 'irregular metamorphosis' and 'retrograde metamorphosis'. The changes seen in roots and tubers under domestication, 'as when the fibrous root of wild celery becomes round and fleshy', are instances of what is meant by irregular metamorphosis in the plant kingdom. Instances of retrograde metamorphosis include the retroversion of petals to leaves (seen in the cowslip), of stamens to petals in the double rose, and certain changes in diseases of plants. In retrograde metamorphosis the 'function, quality, and character of an organ are subverted, not from the intrusion of elements wholly foreign to an organism, but in consequence of the displacement of natural elements, by others of a prior or lower type'. In 'irregular metamorphosis' parts become checked or stunted in their growth or, on the contrary, 'unnaturally exuberant'. He hopes to apply these categories of change to animal tissues. For, says Addison, all tissues of the animal body 'originate from the metamorphosis of cell-organisms in the embryo; are nourished by the metamorphosis of cell-organisms in the blood,—and are displaced, interrupted, or go back again to cell-organisms in scrofulous

disease, phthisis and ulceration'. He does not hope to explain the 'epigenesis' of cells, i.e. give the reasons why they undergo such changes. He will only endeavour to prove, by microscopy, that 'in consumption and scrofulous disease, cell-organisms, characteristic of embryo structure and of blood, reappear amongst and supplant the elements characteristic of the healthy adult texture'.[6] We find also that Addison has acquired—in addition to the new idea represented by the term metamorphosis—a new term for the content of 'plastic' material within the colourless cells of the blood. The new term is *protoplasma*. Following von Mohl, the viscous granular matter discharged from colourless cells either under the influence of various reagents or spontaneously during the coagulation of the blood, and thereafter capable of giving rise to fibrous structures, may be called protoplasma. The 'colourless elements of blood may be considered as consisting of cells and protoplasma'.[7]

In our examination of the book and series of papers we need take note only of those points at which Addison supplements, amplifies or otherwise changes his earlier presentations. Firstly, with respect to the structure of capillaries, he now states that there are two types, fibrous and corpuscular, with many intermediates. Fibrous capillaries are bounded by 'waved or straight fibres, enclosing nuclei, and there are few or no spherical cell-organisms to be detected'. Such capillaries may be seen in the *pia mater*, the omentum, and in the areolar structures generally. Corpuscular capillaries are 'bounded by cell-organisms or epithelial particles several ranks deep' and may be found in the 'corpuscular secreting structures'.[8] In the embryo all textures are corpuscular, that is composed of cells, and all 'blood-currents' are bounded by cells. Later on in the development of the embryo one finds fibres scattered among these cells. At a still later stage the cells are absent or inconspicuous, if the capillaries are to become those of the fully fibrous variety.[9] But when inflammation takes place in serous and fibrous textures of the adult organism (such as the pleura, peritoneum and *pia mater*) one sees the fibrous capillaries

revert partially to the corpuscular type. The fibres give way to or are overgrown by cells. The tissue is now, says Addison, in a 'state of retrograde metamorphosis, for it has returned to a condition analogous to that in which it was, in the early embryonic state'.[10] He notes that, in general, all corpuscular or secreting textures (the liver, brain, etc.) are supplied by corpuscular or 'nutrient' capillaries, whereas the supporting fibrous and serous connective tissues, the function of which is 'more mechanical or ministerial', have relatively few such.[11]

Addison now uses the concept of metamorphosis to make more explicit what was formerly less so. There are, he says, two chief phenomena to be observed in the nutritional process. The first is 'the abstraction of the general elements from the circulating current', and the second 'the metamorphosis of these elements whereby they incorporate with the special texture'. The phrase 'general element' refers, of course, to the white cell. As Addison puts it, 'the elements of the blood, then, administering to growth, are colourless cells and protoplasma'—the latter contained within the cells. The interchange between blood and tissue is not, as most physiologists and pathologists suppose, a 'species of exosmosis, through a structureless membrane, with the genesis of cells from germs in the exudation, but a phenomenon of morphology'.[12] The nutritive material is furnished to the tissues in corpuscular form. In inflammation an excess of nutritive material is in this way brought to the inflamed part. Whether the excess will be helpful or harmful to the organism is another matter. Its positive aspect is seen, for example, in the healing of wounds and the union of broken bones, its negative aspect in scrofula.[13] The majority of writers on the subject of scrofula, says Addison, describe certain general features of the body that they take to be characteristic of the scrofulous 'diathesis', that is of a certain inherent disposition or complexion of the body predisposing to the development of overt scrofulous change. But in his opinion 'structure must exist before its qualities can be known; so it is evident that the morphological phenomena must be the

antecedents, of which the constitution or diathesis is the consequent'.[14] In the scrofulous change termed tubercular consumption, or phthisis, the most constant morphological feature is the tubercle. The 'semi-transparent granulations' that are the first stage of tubercle are found in the serous and fibrous textures as well as in the corpuscular. What is the nature of tubercle? It is not, says Addison, an amorphous exudate that has subsequently undergone cellular development. The granulations are composed of outwandered colourless cells. When they occur in fibrous textures (such as the peritoneal surfaces, omentum and *pia mater* of the brain) the adjacent capillaries are seen to be bounded by cells instead of fibres.[15] So much we have been told before. The only difference is that Addison now makes use of the notion of metamorphosis. For in the 'transformation of these granulations into opake tubercles or tuberculous matter there occurs a retrogradation of the natural textures surrounding the tubercles' analogous to retrograde metamorphosis as seen in plants.[16]

As for ordinary, non-scrofulous, inflammation, Addison passes over the subject rapidly, for he has little to add that he has not said many times before. He emphasizes the fact that inflammation is 'not altogether dependent on the quantity of red blood in the part, nor on the quickness and slowness of the circulation, nor upon enlargement or diminution of the calibre of the vessels, but upon an increased amount of stationary colourless corpuscles and protoplasma preceding an active morphological change'. Like Bennett, he recognizes that similar vascular changes occur in circumstances that have nothing to do with inflammation.[17] One important new point is made by implication. Addison says that the white blood cells are, as it were, embryonic forms from which the elements of the special textures originate and 'to which microscopical anatomy proves they are disposed to revert in scrofulous disease and ulceration'. This statement implies that some of the cells (all of which Addison formerly interpreted as recent migrants from the bloodstream) in such lesions are local cells that have undergone retrograde

metamorphosis. But Addison does not develop this suggestion.[18]

It is in this book that we come across the passage that will be repeated by Cohnheim in 1867, at the instigation of Virchow, and by Addison's obituarist in the *Medical Times and Gazette* of 1881. 'Lastly,' states Addison, 'during inflammation—using the word in the general sense here indicated—there is more or less marked increase of colourless elements and protoplasma in the parts affected. At first—*in the first part*—these elements adhere but slightly along the inner margin or boundary of the nutrient vessels, and are therefore still within the influence of the circulating current; belonging, as it were, at this period, as much or rather [*sic*] to the blood, than to the fixed solid. Secondly—*in the second stage*—new elements appear at the outer border of the vessels, where they add to the texture, form a new product, or are liberated as an excretion'.[19] It is perhaps unnecessary to emphasize that nothing has changed in this account since Addison first classified it as hypothesis rather than observed 'fact'. Anxious as he was for corroboration there is little doubt that he would have acknowledged Waller's actual observation of the outward passage of white cells had he known of it.

Addison's book was received coolly, as might be expected, by the *British and Foreign Medico-Chirurgical Review*.[20] Admitting that the book, like everything from Addison's hand, displayed 'not a little originality of thought and observation', his critic found it, on the whole, confused in arrangement and clumsy in expression. Old ideas were draped in pretentious new language. What was new was not true and what was true not new, said the anonymous writer. Addison's 'peculiar views of the process of nutrition' were there as usual. The reviewer could assent neither to Addison's description of the two types of capillaries and the nature of their walls nor to the assertion that 'pus-cells, granulation-cells, epithelia, etc. are all merely altered colourless blood corpuscles, which have worked their way to the outside of these vessels'. The identification

of the inflammatory process with the processes involved in scrofulous change seemed acceptable up to a point. But in what the reviewer called the quiet substitution of scrofulous material for the natural textures, 'as when tubercular matter is . . . silently deposited in the lung parenchyma', he found all of the essential characteristics of inflammation wanting.[21] Addison's supposedly new idea, that of retrograde metamorphosis, struck the reviewer as suitable enough, insofar as certain scrofulous changes were concerned, but he added that it was 'no novelty'. The treatment of Addison's book in the *London Medical Gazette* was, equally predictably, much more favourable. None of the controversial points of Addison's doctrine was faced. The reviewer limited himself to an outline of its contents and the statement that the book would no doubt be given the 'high rank in the literature of our profession which it richly deserves'.[22] In fact, however, it seems to have attracted very little additional attention.

Mention has already been made, in connexion with Waller, of Arthur Hassall's book on normal and abnormal microscopic anatomy.[23] Although Hassall's book contains no reference to Addison's publications of 1847 or 1849 it merits recall here both for the wide and sustained publicity it gave to Addison's views (in the United States as well as in England) and for its rejection of the stone on which Addison's entire theoretical structure was based, namely, the outward passage of white cells from the blood to the tissues. Hassall had at first been inclined, he wrote, to place some credence in Addison's views on this point. But he eventually came to the conclusion that 'the direct passage of the white corpuscles of the blood appears never to have been clearly witnessed'.[24]

Bibliography and Notes

1. A brief letter from Addison, dated 14 July 1845, appears in the *London Medical Gazette* (New series, vol. I, 1845, p. 570). In it he describes 'two distinct kinds of colourless cells to be detected at all times in human

blood'. His procedure is to dilute with an equal volume of water a drop of blood pricked from the finger and placed on a glass slide. The drop is then covered with a thin slip of glass and examined at a magnification of 700 to 900 diameters. Addison made out (1) colourless cells with 'a large round, single and well-defined nucleus' containing a 'multitude of barely perceptible molecules', and (2) colourless cells containing a smaller number of 'larger, darker, and coarser particles mingled with bright granules, in the midst of which the nucleus may, or may not, be visible; if visible it is sometimes single, sometimes double'. Intermediate forms were also present. Addison's description is certainly on a level with any available at the time. More precise differentiation of the various types of white blood cells had to await Ehrlich's introduction of *Farbenanalyse* in the eighteen-seventies, using aniline dyes (cf. Appendix B).

2. William Addison, 'The law of the morphology or metamorphosis of the textures', *Prov. med. surg. J.*, 1847. Eleven separate papers, comprising fifteen articles, appeared irregularly from 27 January to 22 September, as follows: I. Vegetable textures, pp. 33–36; II. Animal textures, pp. 60–62; III. Embryonal and adult textures; IV. Structure of blood-vessels; V. Structure of lungs; VI. Physiological analysis of the corpuscular, cellular and fibrous textures, pp. 90–93; VII. The process of nutrition, or the reciprocal action between the blood and the solid textures; VIII. Inflammation, pp. 116–21; IX. Scrofula; X. Seat and nature of tubercles in the lungs; XI. Structural changes produced by scrofulous disease, pp. 169–71; XI. (concluded), pp. 199–203; XII. Regular, irregular, retrograde, and ascending metamorphosis in the textures of plants, pp. 229–31; XIII. Regular, irregular, retrograde, and ascending metamorphosis in animal textures, pp. 259–63; XIV. Inflammation considered morphologically, pp. 313–15; XIV. (continued), pp. 340–42; XIV. (concluded); XV. Sthenic and asthenic inflammation; acute and chronic disease, pp. 505–9.
3. William Addison, *On Healthy and Diseased Structure and the Principles of Treatment for the Cure of Disease, Especially Consumption and Scrofula; Founded on Microscopical Analysis*, London, 1849.
4. Addison refers here to Lorenz Oken's book *Die Zeugung*, first published in 1805: 'The fact that the material elements of all beings—plants and animals—originate from minute cell-organisms' was, writes Addison, 'first announced by Oken; it has been ably illustrated and enforced by Schleiden, Schwann, Barry and other physiologists' (op. cit., p. 2). Since Addison always referred to English translations of German works when he quoted from the text it seems unlikely that he had read Oken. In any case his attribution makes sense. The cell theory that took form in the early nineteenth century rested as much on the observation of minute forms of life, the so-called infusoria, as it did on the observation of little boxes, *à la* Hooke. Oken held that the begetting of plants amoun-

ted to a synthesis of infusorial organisms. Begetting involved an increase in size, and infusoria could do so only by increasing in number and arraying themselves together; *all* organic begetting is a synthesis of infusoria, said Oken (*Die Zeugung*. Bamberg/Würzburg, 1805).

5. *On Healthy and Diseased Structure*, pp. 15–20. Addison says that morphology, the study of the transformation of the cells of the embryo plant into the various organs of the adult has long been a branch of physiological botany, having been introduced by Linnaeus and furthered by Goethe. He cites Lindley's *Introduction to Botany* and Linnaeus' *Systema naturae*.
6. Ibid., pp. 9, 17–20. In articles XII and XIII (Cf. Note#2) Addison includes a fourth type of metamorphosis, the 'ascending'. This is said to occur in plants when structures 'pass above or beyond, the natural type—as when the sepals of the calyx assume the colour and textures of a petal—when petals assume the form and function of stamens—or when stamens become ovaries' (op. cit., p. 231). He offers no instance of ascending metamorphosis in animals. This notion, or one closely related to it, is expressed today by the term 'prosoplasia', defined as the abnormal differentiation of tissue or its development into a higher state of development or function (Dorland's *Medical Dictionary*, 24th ed., Philadelphia and London, 1965, p. 1229). The current term 'metaplasia', defined as the change of adult cells within a tissue to a form not normally present in that tissue (Dorland, op. cit., p. 908) applies more generally to Addison's remarks on metamorphosis. (The term metaplasia was introduced by Virchow in 1871 in the 4th ed. of *Die Cellular Pathologie*: 'Hier handelt es sich also um eine Gewebsumwandelung (Metamorphose, Metaplasie)', op. cit., p. 70; and in 1884 his paper 'Ueber Metaplasie' was published in the *Arch. path. Anat. Physiol. klin. Med.*, **97**, 410–30).
7. Ibid., pp. 26–27. The strange phrase 'cells and protoplasma' is due to the fact that it was still possible for Addison to think of the 'cell' as a container divorced from its content. This also accounts for his use of the term 'cell-organism'. It is sometimes said that the 'cell' and its 'content' did not fully unite until the publication, in 1861, of Max Schultze's paper defining the cell as a clump of protoplasm containing a nucleus ('Ueber Muskelkoerperchen und das, was man eine Zelle zu nennen habe', *Arch. Anat., Physiol. wiss. Med.*, Jahrgang 1861, pp. 1–27). But Schultze's paper marks a terminological rather than a conceptual shift. Thereafter 'cell' means 'cell-as-a-whole', which is also the meaning of 'cell-organism'. As for the term 'protoplasma', Addison cites a paper by Hugo von Mohl (1805–1872) that had appeared in translation, he says, in the *Annals and Magazine of Natural History*, July, 1846. To Addison's remarks it may be added that before von Mohl the term 'protoplasma' was used by Jan Purkinje on a single occasion in 1839, in reference to the 'protoplasma of the embryo'. Von Mohl used this (originally theological) term seven years later to designate a fluid, granular substance capable of giving rise to solid structures. Its

conceptual relationship to blastema and cytoblastema is obvious. But we must bear in mind that for Addison protoplasma does not form cells, but rather the reverse, for 'all fibrous structures originate in gelatinous protoplasma . . . and this again from corpuscles or cells' (*On Healthy and Diseased Structure*, p. 31).

8. Ibid., pp. 31–32. If we examine Plate III in the book, illustrating Addison's corpuscular capillaries in the choroid plexus, tongue and intestinal villi, we see that he assigns the surrounding or adjacent cells the role of capillary wall, bounding the capillary proper. The latter he sees as a mere channel between the cells.
9. Ibid., p. 33. Plate I., fig. 5 illustrates such a vessel in the foetal hare.
10. Ibid., p. 35.
11. Ibid., pp. 36–38.
12. Ibid., pp. 41–44.
13. Ibid., p. 45. In art. VII (op. cit., p. 119) Addison uses his new terms with a vengeance, writing that 'simple healthy inflammation consists of an increased amount of protoplasma with a conformable morphology; and destructive unhealthy inflammation, of an increased amount of protoplasma with an unconformable morphology'. He adds that healthy inflammation closes wounds, repairs fractures and has a healing tendency. In this way 'two very different, nay opposite and incongruous things are brought together under the unscientific and silly term of inflammation'. Here Addison was following Magendie, Andral, Lotze and others who objected to both term and concept of inflammation.
14. Ibid., p. 50
15, Ibid., pp. 61–62.
16. Ibid., pp. 63–64. Addison says that his findings corroborate those of Schroeder van der Kolk, Guillot and Bennett but show also that 'the great vascular transformation, and villous growths they speak of, are the features or accompaniments of a great metamorphosis of the pulmonary parenchyma, in which the simple fibrous, non-secretory respiratory capillaries, and normal structure of the lung, assume an early corpuscular or embryonic type, with an occlusion of the air spaces'.
17. Ibid., pp. 75–76.
18. Ibid., pp. 78–79.
19. Ibid., p. 82. Addison no doubt meant to write 'as much or rather more to the blood', and so the passage appears in the *Medical Times and Gazette*. In Cohnheim's footnote of 1867 the word 'more' does not appear. The passage is not to be found in the *Provincial Medical and Surgical Journal* series. With respect to the formation of pus in this way Addison says (art. XIV, loc. cit., p. 340) that Vogel 'considers it unnecessary to refute the doctrine', referring to p. 287 of Vogel's newly-translated treatise (German original, 1845) on pathological anatomy (Julius Vogel, *The Pathological Anatomy of the Human Body*; trans. from the German with additions, by George E. Day. Philadelphia, 1847).

There is no reference to the matter on the page cited by Addison, but on p. 143 Vogel has this to say: 'It is scarcely necessary to observe that most of the opinions that have been promulgated regarding the formation of pus are undeserving of serious refutation; as, for instance, the view maintained by Gendrin that pus-corpuscles are nothing more than modified blood corpuscles.' Gendrin's ideas on the subject, says Vogel, have been revived recently by Braun, von Bibra and Barry, but without any new evidence in favour of them (Vogel does not mention Addison). Vogel then gives what in his opinion can be 'seen': 'the above described mode of formation of pus-corpuscles from a fluid cytoblastema has been directly observed, whilst on the other hand, no one has ever yet succeeded in following under the microscope the conversion of blood into pus-corpuscles'. Addison, however, can find in Vogel's book or in Bennett's treatise on inflammation, 'no proof whatever that coagulated fibrin acts as a cytoblastema—no demonstration of its evolving muscular fibres, nervous fibres, granular cells or pus' (loc. cit., p. 340–41). And he repeats, once again, that when blood coagulates fibres can be seen to form in the plasma, but there is no sign of cell genesis.

20. Unsigned review in *Brit. for. med-chir. Rev.*, 1849, **4**, 220–26.
21. Ibid., p. 225. What these essential characteristics are the reviewer does not state, but he seems to have had in mind the symptomatic (redness, heat, swelling and pain) or the vascular. He says that Addison's account is perhaps applicable to scrofulous inflammation, that is to 'inflammation occurring in the scrofulous constitution, and modified by the scrofulous diathesis'.
22. Unsigned review in the *London Medical Gazette*, 1849, New Series **9**, 161–63. Where the *Brit. for. med-chir. Rev.* dismissed Addison's section on 'practical psychology' with an exclamation mark enclosed in parenthesis, the *London Medical Gazette* spoke with implied approval of 'Dr. Addison's observations on the phenomenon of hysteria, and the influence of mental emotion in the causation and treatment of disease and the preservation of health' (Cf. Appendix A).
23. Cf. Chapter II/4 and Note #2 therein. The 1849 edition of Hassall's book appeared in separate parts between 1846 and 1849. An unchanged version of the text with additions and an introduction by Henry van Arsdale was published in the United States six years later (New York, 1855), Waller's findings not being among the additions. The index lists the following with respect to Addison: (1) 'his belief in the existence of a nucleus in the red blood disc', (2) 'views on the structure of the red blood corpuscle', (3) 'observations on the white corpuscles of the blood', (4) 'further observations on the same', (5) 'his opinion that milk, mucus, and bile are the visible fluid results of the first dissolution of the cells', (6) 'his opinion that the white corpuscles are the foundations of the tissues and the special secreting cells', (7) 'on the presence in increased quantities of the white corpuscles in the hard and red basis of boils and pimples, and in the

skin in scarlatina', (8) 'his opinion that mucous and pus globules are altered colourless blood corpuscles', (9) 'his opinion that out of the white corpuscles of the blood, all other corpuscles met with in the body are formed', (10) 'on the action of liq. potass. on pus', (11) 'on epithelial scales in the air cells of the lungs', (12) 'on tuburcles [*sic*] of the lungs'.

24. Hassall, op. cit., 1855, p. 177.

III The Era of the New Cell Theory

III.1 The Decline of the Blastema Theory

Virchow's Cellular Pathology

With increasing conviction Addison continued to reject the blastema theory throughout the latter half of the eighteen forties, and in doing so he stood almost alone among physiologists and pathologists. The reason he gave for his stand was always the same: Neither in the tissues nor in the coagulating blood had the formation of cells from an amorphous or finely granular blastema been convincingly described. Yet we must remember that at the same time there were many investigators convinced that the formation of cells in just this manner was the only conceivable explanation for what they did see under the microscope.

In 1871, at a time when the blastema theory had lost all but a vanishingly small number of adherents, Virchow looked back at the not so distant past when his mind was, as he wrote, 'dominated by the blastema theory'. He commented that Henle, in his early studies of epithelial cell formation, had almost obtained a correct understanding of the fact that cells arose only from pre-existing cells but had been so much under the influence of the ruling theory that he had hypothesized the existence of a layer of blastema between the connective tissues and the overlying epithelium of skin and mucus membrane surfaces.[1]

Henle himself looked back on those same years on the occasion of delivering an obituary on Schwann in 1882.[2] He admitted that the belief in the development of the solid components of animal tissues from a fluid, plastic substance

had 'struck its roots too deeply' for anyone at the time to have doubted that cells actually arose in this way. Schwann himself, said Henle, had approached the correct view when he raised the question whether the cleavage of the yolk in fertilized eggs might not represent a cell formative process. But Schwann's progress along this line of thought had been blocked by the poorly understood relationship between yolk, ovum, germinal vesicle and developing embryo.[3]

But it is not true, as Virchow and Henle imply, that everyone bowed down before the blastema theory insofar as the formation of cells was concerned. Reichert, for example, in 1841 called Schwann's concept of the cell as the common developmental principle of animals and plants a 'great discovery', but as for the theory of formation of cells from a cytoblastema he was, and remained, sceptical. Reichert's own embryological studies on spiders, crabs, snails and mammals had convinced him that the embryo was constituted by cells, and cells only. The formation of new cells in a free extracellular 'cytoblastema' did not square with his own experience, at least as far as the early stages of the development of the embryo were concerned.[4] It is also true that among botanists the belief that cells arose from preexisting cells rather than from an extracellular blastema had been widely favoured for a considerable length of time before the eighteen fifties. This is evident in von Mohl's monograph of 1853 on the vegetable cell in Wagner's *Handwoerterbuch*.[5] Von Mohl's account is as follows. In 1835 he himself had published the first accurate study of the multiplication of cells by division and attempted to set aside older accounts of the manner in which new cells were formed. New cells, according to his findings, were derived from 'mother cells', the process involving the gradual appearance of a transverse wall that eventually divided the cell content into two more or less equal halves. Later, after having distinguished the cell 'membrane' from the cell 'wall', he had obtained a firmer grasp of the meaning of these events. But, continued von Mohl, Schleiden's paper of 1838 then

appeared with its claim that 'free cell-formation', i.e. the formation of cells in a structureless cytoblastema, was the only way in which new cells originated. Botanists were thereby led along a mistaken path.[6] Von Mohl's account is misleading, for he fails to distinguish sharply enough between the free formation of cells from an *extracellular* cytoblastema and their formation in the same way from an *intracellular* cytoblastema. Schleiden had in fact favoured the formation of new cells within older cells rather than free extracellular formation, although he had indeed taken the latter into account.[7]

It was von Mohl's opinion in 1853 that new cells formed in two ways only, (1) by the division of pre-existing cells, (2) by the free formation of daughter cells within the cavities of mother cells.[8] In reading his account one finds evidence of a conceptual conflict. The notion of the cell as a container, essentially constituted by its walls, was struggling with two other notions. One emphasized the essentiality of the cell content, while the other laid stress on the cell-as-a-whole, a discrete entity or living unit bound up (in German thought, at least) with the Leibnizian 'monad'. If we regard the 'cell' as a mere container there is little difference whether new cells form from a cytoblastema lying within *or* beyond its wall. On the other hand, if we regard cells as discrete living entities there is a very great difference between the free formation of cells from an extracellular blastema and the formation of cells within, or by division of, pre-existing cells. The former, in fact, amounts logically to the admission of spontaneous generation, *generatio aequivoca*, as was clear to many investigators of the time.[9]

Among those primarily concerned with animal rather than plant tissues and engaged in re-evaluating the blastema theory in the late eighteen forties and early fifties we find several former pupils of Johannes Müller, the most important of whom were Kölliker, Remak and Virchow. Schwann was not among them. He had been called to a professorship at Louvain in 1839 and his brilliantly productive early years succeeded by a long period of quiescence.

Müller himself took no part in the re-evaluation. He died in 1858, the year of the publication of Virchow's book on cellular pathology.

Rudolf Kölliker made a major contribution to the problem of cell genesis in his studies of developing embryos. He came very close to a solution of the puzzle of the relationship between the 'cleavage-spheres' of the fertilized ovum and the 'cleavage-cells' of the later embryo, when he identified both as instances of one and the same process. But Kölliker's statement of 1844 that he could find 'in the entire line of development of tissues in animals, just as in plants, no formation of cells other than from those already present' does not mean all that it may seem to mean. For we find Kölliker writing a few years later in his textbook of histology (1851) that in the adult the free formation of cells in pathological exudations is of very common occurrence, although under normal conditions it is far less common than ordinarily assumed.[10] The step that Kölliker had failed to take on the path away from the blastema theory was taken in 1852 by Robert Remak.[11] More correctly than von Mohl he noted that Schleiden had regarded the extracellular origin of new cells in a cytoblastema as apocryphal, along with the majority of botanists of his time.[12] Schwann, in contrast to Schleiden, had then proposed to give extracellular free formation of cells in animal tissues equal rank along with intracellular free formation.[13] Remak stated that as for himself the extracellular origin of cells had, from the beginning, seemed an event as improbable as the occurrence of spontaneous generation. His own studies of the development of the embryo, along with those of Kölliker, had led him to the conclusion that the puzzling cleavage-spheres of the yolk (the protoplasma of the egg-cell, according to Remak) were simply cells in the process of multiplication by division. At no time in the progressive division of cells in the developing ovum or later in the embryo were 'naked' nuclei or an intercellular blastema to be found, and at no time did the extracellular formation of nuclei take place. The final step was taken when Remak announced that cells

did not form in an extracellular cytoblastema under normal *or* pathological conditions.[14]

Karl Reichert, who from the first had denied the extracellular free formation of cells, called in 1854 for the complete elimination of blastema theory from physiology and pathology.[15] Not a single confirmed instance of extracellular free formation could be pointed to in animals or plants, he wrote, and studies of embryonic development had shown conclusively that every cell was derived from the fertilized egg-cell. This in turn came from a parent organism, where it had arisen as the descendant of another cell.[16] He called also for a re-evaluation of pathological tissue formation in the light of the new theory of cytogenesis. Diseases represented nothing more than 'life under abnormal circumstances'.[17] Pathological anatomical changes should be considered as 'altered morphological relationships of the healthy body'. The questions to be answered by the pathological anatomist were (1) what morphological constituents of the affected organ have changed? (2) in what consists this change? and (3) how did the change come about?[18]

Reichert's call received a response from Virchow in the following year. As we examine Virchow's paper of 1855, entitled 'Cellular Pathology' we find that the new way of viewing disease processes offered therein is based on a group of assumptions each of which had already been set forth by someone other than Virchow himself. His contribution was in the main a synthesis of these assumptions, although he did contribute also to the store of evidence that had made them increasingly acceptable to many other investigators.[19] But this is not the entire story, for a truly cellular pathology was not possible until the widely held idea that in certain parts of the body cells were present only during embryonic life (giving way in the adult to other structural elements) could be set aside. And still another difficulty was present. The considerable importance accorded to the animal cell as a structural, functional and developmental unit by investigators in the mid-forties did not mean that they regarded

the cell as an autonomous unit. It would be closer to the truth to say that the animal cell (not necessarily the plant cell) had rather the status of a cog in a machine. The meaning and existence of the cell were acquired by virtue of its place within the whole. Expressed in the language of the time the cell did not bear within itself the laws governing its existence. Virchow, with the aid of an idea that he acquired from John Goodsir, helped give the cell the required existential status.

The *Anatomical and Pathological Observations* of the Scot, John Goodsir, appeared in 1845.[20] In this book he put forward the claim that cells, in addition to their role as structural and functional units, were centres of nutrition as well. He argued also that cells were present in adult organisms to a greater extent than had heretofore been supposed. 'By centres of nutrition,' wrote Goodsir, 'I understand certain minute cellular parts existing in the structures and organs.' He was 'inclined to believe in the general existence of such centres, for a certain period at least, in all textures and organs'.[21] Goodsir's second idea was as follows. Beginning with a primary nutritive centre (which was the fertilized egg-cell) the organism took form by the successive development of secondary cell centres. Thus there was a 'division of the whole into departments, each containing a certain number of simple or developed cells, all of which hold certain relations to one central or capital cell, around which they are grouped'. This central cell was the 'mother of those within its territory'.[22]

Virchow subscribed to one part of Goodsir's double thesis in his essay of 1852 entitled 'Nutritional Units and Foci of Disease'.[23] This part was 'the originality of the idea that the cells of the developed body and not merely of the body in the process of formation possess independent life and represent relatively independent centers of nutrition and secretion'.[24] Virchow himself had been broadening the scope of the cell idea in adult organisms by his studies of bone, cartilage, ligaments and subcutaneous connective tissues. Together with Reichert, who shared many of his views on

this subject, he had sharply distinguished the intercellular or 'ground' substance from the substance of the connective tissue cell proper.[25] He was in this way able to extend Goodsir's concept of the cell as a nutritive centre to a part of the body hitherto thought to have lost its cellular character during the transition from embryonal to adult life.

In addition to the geographic extension of the scope of Goodsir's 'nutritive centre' Virchow superimposed on that centre a series of higher nutritive units, each comprising cells, vessels and nerves. Goodsir had stated that the nutritive centre, anatomically considered, was merely a cell. Virchow agreed but pointed out also that while the relatively sovereign cells possessed a certain degree of independence they were nonetheless bound together by the vascular and nervous systems into successively higher unities. The 'dependence of the individual centres of life on the continuance of their mutual relationships and interchanges' explained the overall unity of the animal organism. Otherwise, he said, the body of an animal would be a mere aggregate, or clump, of cells. In the higher animals these cell-blood-nerve units first made themselves manifest. The simplest form of the unit was a group of cells and their surrounding 'ground' substance together with a single capillary and possibly a single nerve fibre (as found for example in the dermal papillae). These Virchow called 'anatomical units'. A focus of disease, so considered, was constituted by a disturbance in the fluid interchanges of single cells, groups of cells or anatomical units with the remainder of the body.[26] From this point Virchow went on to consider disturbances involving still higher anatomical units of the same character (such as those in the heart muscle caused by blockage of flow in the coronary arteries) which do not concern us here. Virchow's anatomical units, it should be noted, were fundamentally vascular units (as he himself pointed out), in consequence of his unwillingness to allow nerve fibres any trophic or nutritive influence over cells in the areas supplied by them.

We have, in effect, arrived at cellular pathology. In Virchow's essay of 1855 bearing that title the foundations of

the new doctrine are stated briefly and defended against rival doctrines—chiefly against neural pathology, to a lesser extent against humoralism (represented by the blastema theory). Virchow's cellular pathology involved a radical and complete break with blastema theory and that aspect of Schwannian cell theory. The break is marked by his use of the word 'all' in formulating the basis of the new doctrine: 'All cells are derived from other cells' and 'All diseases are in the last analysis reducible to disturbances, either active or passive, of large or small groups of living units whose functional capacity is altered in accordance with the state of their molecular composition and is thus dependent on physical and chemical changes of their contents', and 'All pathological formations are either degenerations, transformations, or repetitions of typical physiological structures'. He states that 'all physiological activity' is in the end traceable back to the cell, thus opening the door for Max Verworn's explicitly cellular physiology which was to make its appearance a few decades afterward.[27] 'Cellular pathology,' wrote Virchow in 1856, 'seems to me to be the final solution of the thousand year old battle between humoralism and solidism.' He then added, making use of his favourite political metaphor, that in undertaking to 'defend the rights of the third-estate of the numerous small elements it might appear as if the aristocracy and hierarchy of blood and nerve would be shaken at their very roots'.[28] But he meant only to assert the equal rights of those humble citizens the cells.

In 1858 Virchow's book *Die Cellularpathologie*, twenty lectures in which he documented the thesis of his essay of 1855, was published.[29] The second German edition (1859) appeared in English translation in 1860.[30] Bearing in mind that Virchow's rejection of the blastema theory was supported by the most advanced work in German biological science we can perhaps estimate from some of the criticism that he received in England how little chance of success Addison, a relative outsider working more or less in isolation, had actually had in his own attack against the blastema theory in the eighteen forties. The reviewer of Virchow's

book in the *British Medical Journal* of January 1861, after noting that cellular pathology rested on the claim that all cells arose from pre-existing cells, inquired into the evidence for this revolutionary claim.[31] It rested chiefly, he said, on Virchow's identification of the progressive division of the yolk in the fertilized egg with the progressive division of a single cell. Yet, added the reviewer, 'every other embryologist' is of the opinion that after the entry of the spermatozoid into the yolk it, together with the female element—the germinal vesicle—undergoes dissolution. The cells that subsequently constitute the embryo thus arise from the yolk-blastema, rather than from the original germ cells. He admitted that once cells had been formed in this manner they might increase in number by endogenous multiplication. But what, he asked, were we to say of the formation of new cells in the adult organism under pathological conditions if we accepted Virchow's thesis? We find no pus cells in healthy tissues. Where then do the pus cells take origin if we reject the theory of the blastema? Virchow hopes to derive them from the connective tissues or epithelial surfaces. Virchow claims, the reviewer tells us—citing a passage from the book—that we may 'substitute for the plastic lymph, the blastema of the earlier, the exudations of the later writers, connective tissue . . . and directly trace to it, as the general source, the development of new formations'.[32] And among these new cellular formations are pus cells, cancer cells and so on. Virchow then tries to transform the blastema into an 'intercellular substance', continues the reviewer. But 'the truth is, that this intercellular tissue of Virchow is the blastema of Schwann, and gives origin to cells in the manner correctly described by the latter distinguished observer'.[33] 'On the whole', he concludes, 'this attempt of Professor Virchow to revolutionise pathology . . . is a complete failure.' Furthermore, Virchow had taken the leading idea of his cellular pathology from John Goodsir, just as he had appropriated Bennett's work on leukaemia a few years earlier.[34]

In the same year a much more friendly reception was

accorded to Virchow's book in the *Edinburgh Medical Journal*.[35] Its author also emphasized the crucial position occupied by Virchow's interpretation of the connective tissues in relation to the origin of pus cells. The usual doctrine was, he wrote, that pus cells arose *de novo* in a blastema exuded from the small blood-vessels, but Virchow's derivation of all cells from pre-existing cells made this doctrine no longer tenable. Instead, Virchow maintained that pus cells on epithelial surfaces were derived by division of deeply placed epithelial cells, while in the case of the solid organs the formation of pus cells took place in the connective tissue. The reviewer remarked that 'in some respects the theories of Professor Virchow are in advance of the results of actual observation', but called his 'the most remarkable and suggestive book which has appeared in recent times'.[36]

Bibliography and Notes

1. Rudolf Virchow, *Die Cellularpathologie*, 4th ed., Berlin, 1871, pp. 494–95. Virchow's words 'die Blastemtheorie beherrschte die Geister, und wir Alle standen unter ihrer Einwirkung', may be found also in the 1st ed., Berlin, 1858. We shall see later in this section that in 1858 the blastema still 'beherrschte die Geister' in England. On another occasion, in 1877, Virchow remarked that 'nothing was simpler, nothing more logical, nothing more closely in correspondence with the generality of natural-scientific views, than the doctrine of the origin of tissue components from chemical substances, from the so-called blastemas or histogenetic materials' (*Disease, Life and Man. Selected Essays by Rudolf Virchow*, translated and with an Introduction by Lelland J. Rather. Stanford, 1958, p. 146).
2. Jacob Henle, 'Theodor Schwann', *Nach., Arch. mikr. Anat.*, 1882, **21**, xl–xlix.
3. Theodor Schwann, *Mikroskopische Untersuchungen*, op. cit., pp. 46–70. Schwann was uncertain of the significance of the spheres or globules that made their appearance in what he called 'the actual yolk substance'. Are they cells or not? Schwann thinks that they are but is unable to prove it to his own satisfaction. He relied in part on the work of Karl Ernst von Baer, whose paper, 'Die Metamorphose des Eies der Batrachier vor der Erscheinung des Embryo und Folgerungen aus ihr fuer die Theorie der Erzeugung' may be found in *Arch. Anat., Physiol. wiss. Med.*, 1834, pp. 481–509. Von Baer depicts the progressive cleavage of the yolk to a point where about three thousand rounded masses are visible,

whereupon 'a germ separates from the yolk and later, in the germ, an embryo separates from the germinal membrane'. To the modern eye von Baer's drawings show clear evidence of progressive cell division in the yolk.

4. K. B. Reichert, 'Bericht ueber die Fortschritte der mikroskopischen Anatomie in den Jahren 1839 und 1840', *Arch. Anat., Physiol. wiss. Med.*, 1841, pp. clxii–ccxxvii, esp. pp. clxvi–clxviii.
5. Hugo von Mohl, in Rudolf Wagner's *Handwoerterbuch der Physiologie mit Ruecksicht auf physiologische Pathologie*, Braunschweig, 1853, vol. 4, pp. 167–309.
6. Ibid., p. 211. Von Mohl says that Brisseau de Mirbel gave three modes of formation of new cells in plants: (1) *développement interutriculaire*, (2) *développement superutriculaire* and (3) *développement intrautriculaire*, of which he himself admitted only the third.
7. M. J. Schleiden, 'Beiträge zur Phytogenesis', *Arch. Anat., Physiol. wiss. Med.*, 1838, pp. 137–76, esp. pp. 162, 163.

   On p. 167 Schleiden states that in the growth of phanerogamic plants 'cells always form only in cells . . . specifically, I have not at all been successful in reaching a decision on the question whether the tip of the rootlet excretes a fluid in which new cells form'. On p. 161, with reference to the three possibilities of cell formation mentioned by Mirbel, Schleiden states that while Mirbel accepted all three he demonstrated only one, the formation of new cells in pre-existing cells.
8. Mohl, op. cit., p. 211.
9. Virchow remarked in 1898 that the blastema hypothesis 'led to the conclusion that every form of organic tissue or organism, every formation of new cells, must be separated from the preceding by a definite gap (*hiatus*), and that each new formation must be considered a discontinuous vital process'. 'Strangely enough', he continued, 'this . . . was accepted at a time when Darwin was already at work proving that new species arise by the modification of pre-existing forms . . . Schwann's cell theory was in truth a resuscitation of the archaic doctrine of spontaneous generation (*generatio aequivoca, epigenesis*).' In Virchow's opinion Darwin's theory was incompatible with the hypothesis of spontaneous generation and therefore also with the blastema (or cytoblastema) hypothesis (cf. *Disease, Life and Man*, op. cit., p. 225). With reference to Schwann's 'cell theory' Virchow meant, of course, only that part of it bearing on the initial origin of cells from a blastema. Two instances of historical irony present themselves at this point: Schwann's first outstanding piece of scientific work was an attempt to rule out the possibility of spontaneous generation and T. H. Huxley, Darwin's chief spokesman, was at first inclined to regard cells as secondary formations from 'protoplasm', i.e. from a blastema (see note 10 below).
10. Kölliker's statement is quoted from his *Entwicklungsgeschichte der Cephalopoden*, Zurich, 1844. In 1907 Martin Heidenhain called it the

equivalent of Virchow's dictum that all cells arise from other cells (cf. his article in Karl von Bardeleben's *Handbuch der Anatomie des Menschen*, Jena, 1907, vol. 8, pt. 1, p. 16). Kölliker's comments of 1851 may be found in the English translation of *Handbuch der Gewebelehre des Menschen* (*Manual of Human Histology*), by A. Kölliker, trans. and ed. by George Busk and Thomas Huxley, London, 1853, 2 vols., vol. 1, pp. 20, 21. A note by the translators on p. 21 casts doubt on the occurrence of all free formation of cells, normal or abnormal. They write that 'there cannot be said to be any evidence of the occurrence of free cell-development in animals, as long as in any case cited it is not shown that the first-formed particles which make their appearance cannot have derived their origin from pre-existing formed particles, either by the detachment or fission of the latter'. This casts doubt not so much on the free formation of cells as on the free formation of particulates of any kind capable of uniting later to form cells. Adding to the confusion is a statement made by Huxley in the same year (1853) that all tissues are 'the result of the differentiation of a structureless blastema—the first step in that differentiation being the separation of the blastema into endoplast and periplast, or the formation of what is called a "nucleated cell"' ('The cell theory', *Brit. for. med.-chir. Rev.*, 1853, **12**, 221–43). The cells are no more than secondary formations; they are 'not instruments, but indications . . . no more the producers of the vital phenomena, than the shells scattered in orderly lines on the sea-beach are the instruments by which the gravitative force of the moon acts on the ocean . . . the cells mark only where the vital tides have been and how they have acted' (ibid., p. 243). Huxley was concerned to show that 'vital phenomena are not necessarily preceded by organization, nor are in any way the result or the effect of formed parts, but that the faculty of manifesting them resides in the matter of which living bodies are composed . . .' (ibid., p. 243). Evidently Huxley saw a certain degree of incompatibility between the idea of the cell as the unit of life and the idea of protoplasm as the substance of life.

11. Robert Remak, 'Ueber extracellulare Entstehung thierischer Zellen und ueber Vermehrung derselben durch Theilung', *Arch. path. Anat. Physiol. klin. Med.*, 1852, **5**, 47–57.
12. Ibid., p. 47. Remak cites pp. 162, 163 of Schleiden's article of 1838. He mentions von Mohl, Braun, Unger, Naegeli, Hofmeister and Schacht among botanists who favour the origin of new cells in plants by division of pre-existing cells and by free cell formation *within* pre-existing cells.
13. Ibid., p. 47.
14. Ibid., p. 57. Remak's statement is worth quoting in its entirety: 'These results have just as close a relationship to pathology as to physiology. That pathological forms of tissue constitute mere variants of normal embryonic developmental types can hardly still be disputed, and it is not likely that they would possess the privilege of the extracellular origin of cells. The so-called organization of plastic exudates and the earliest

stages of the formation of morbid tumours need an examination in this light. Resting on the corroboration given my doubts of many years, I dare express the opinion that pathological tissues, just as little as normal, are formed in an extracellular cytoblastema; they are, rather, the descendants or products of normal tissues of the organism.'

15. Karl B. Reichert, 'Bericht ueber die Fortschritte der mikroskopischen Anatomie im Jahre 1853', *Arch. Anat., Physiol., wiss. Med.*, 1854, pp. 1–80.
16. Ibid., p. 3. Reichert, too, here equated extracellular free formation of cells with spontaneous generation.
17. Ibid., p. 2: '. . . that in diseases life simply manifests itself under abnormal conditions.' This idea is usually associated with Virchow, who expressed it in 1847 with the statement that diseases are 'only the flow of living phenomena under altered conditions' ('Ueber die Standpunkte in der wissenschaftlichen Medicine', *Arch. path. Anat. Physiol., klin. Med.*, 1847, **1**, 3–19, cf. p. 3).
18. Ibid., pp. 2, 3.
19. Rudolf Virchow, 'Cellular-Pathologie', *Arch. path. Anat. Physiol. klin. Med.*, 1855, **8**, 1–39.
20. John Goodsir. *Anatomical and Pathological Observations*, Edinburgh, 1845, reprinted in *The Anatomical Memoirs of John Goodsir*, edited by William Turner, Edinburgh, 1868, pp. 389–507.
21. Ibid., p. 389.
22. Ibid., p. 390.
23. Rudolf Virchow, 'Ernaehrungseinheiten und Krankheitsherde', *Arch. path. Anat. Physiol. klin. Med.*, 1852, **4**, 375–99.
24. Ibid., p. 383.
25. For Virchow's views on the connective tissues see his *Gesammelte Abhandlungen*, op. cit.
26. Virchow, *Ernaehrungseinheiten*, op. cit., *passim*.
27. Virchow, *Cellular-Pathologie*, op. cit., pp. 14, 15, 23. *Omnis cellula a cellula* is found on p. 23. The 1st ed. of *Die Cellularpathologie*, Berlin, 1858, does not contain the Latin quotation. The 2nd ed., Berlin 1859, contains *omnis cellula e cellula*; the 4th ed., Berlin 1871, *omnis cellula e cellula*. In his 'Die Stellung der Pathologie unter den biologischen Wissenschaften', *Berl. klin. Woch.*, 1893, **35**, 359, Virchow returns to *omnis cellula a cellula*. The French translation, by Paul Picard, of the 3rd ed. of *Die Cellularpathologie* has *omnis cellula a cellula*. In the introduction *omnis cellula cellula* is ascribed to Virchow by the translator, who cites a doubtful reference for authority. He claims also that Remak, in 1852, used the phrase *omnis cellula in cellula* but this, too, appears doubtful.
28. Virchow, *Gesammelte Abhandlungen*, op. cit., pp. 50, 1.
29. Virchow, op. cit.
30. Rudolf Virchow, *Cellular Pathology*, tr. from 2nd ed. by Frank Chance, London, 1860.

31. Unsigned review in the *British Medical Journal*, 12 January 1861, pp. 44–46; ibid., 26 January 1861, pp. 94–96.
32. Ibid., p. 94. The reviewer's quotation, reproduced here in part, comes from p. 398 of Chance's translation.
33. Ibid., p. 95.
34. Ibid., p. 96. The reviewer charges Virchow with the misappropriation of Goodsir's ideas of 'cell-territories' and 'brood-cells', stating that just as Virchow 'derived his leading views as to cells from one Edinburgh Professor, so he has borrowed, and equally without acknowledgement, his notions concerning leukaemia from another, viz., Professor Bennett'. Unlike Virchow, says the reviewer, Goodsir was 'too cautious to pretend that every morbid cell-product could be shown to originate from pre-existing cells'. A formal charge of plagiarism was set forth a few years later by John Goodsir's brother, Joseph Taylor Goodsir, in his *Grounds of Objection to the Admission of Professor Virchow as an Honorary Fellow of the Royal Society of Edinburgh*, Edinburgh, 1868.
35. Unsigned essay review, 'Professor Virchow on cellular pathology', *Edinb. med. J.*, 1861, **6**, 814–26. Here too the fundamental doctrines of Virchow are said to have been 'first clearly stated by Professor Goodsir', but the reviewer finds it enough that Virchow 'gracefully acknowledges his obligations by dedicating to Professor Goodsir his present work'. The German editions, however, were not so dedicated. Joseph Goodsir called the dedication of the English translation to his brother a 'sop to Cerberus' (op. cit., p. 13).
36. Another long and predominantly favourable review of Chance's translation of Virchow may be found in the *Brit. for. med.-chir. Rev.*, 1859, **24**, 209–23. The reviewer sees the problem of the formation of pus as crucial in Virchow's rejection of the blastema hypothesis. He writes: 'Our readers will no doubt at once say, "Are not pus cells formed on free surfaces—such as mucous membranes or the pleura, or in the interior of solid organs; and is not this from transformation of what was at first an amorphous exudations?" "Not so," reply Virchow and his followers; "every pus cell arises from a previous cell, it in no cases originates *de novo*; your notion of a fibrine-looking plasma poured out on a mucous membrane or on the pleura, and forming pus by internal changes, is an entire mistake. Omnis cellula e cellula".' The reviewer expresses the opinion that Virchow has been somewhat too anxious to break with the old doctrines and has mixed truth in with hypothesis in doing so.

III.2 White Blood Cells as Physiological and Pathological Agents

Addison's *Cell Therapeutics* (1856)

In Addison's book of 1849 on healthy and diseased structure there is a passage that turns up seven years later on the title-page of his new book, *Cell Therapeutics*. It reads as follows: 'If results derived from microscopical researches be incorporated in the science of physiology, and be received in explanation of appearances in morbid anatomy, they must also be admitted into the domain of therapeutics.'[1] In other words a cellular physiology and a cellular pathology imply a cellular therapy. The cell doctrine, Addison states in *Cell Therapeutics*, has gained a stronghold in pathology as well as in physiology. And, he adds, 'if cells and nuclei are of such generality and importance as to take rank as agents in normal growth, so that ALL healthy changes of structure and function be referred to them, they can hold no inferior rank, being present in all therapeutical reactions against injuries and diseases'.[2] From what we know of Addison's persistent rejection of blastema theory in the eighteen forties —culminating in his claim that cells arise only by the division of pre-existing cells and demand that the doctrine of the blastema be abandoned entirely[3]—we might expect that the eighteen fifties would prove to be in some measure the decade of his triumph, in which at least one of the ideas he had so strongly championed at last became established. But this expectation on our part, if it exists, is doomed to disappointment. For not only does Addison fail to give any sign of awareness that the supports of the blastema theory are being weakened by the onslaughts of such men as Kölliker, Remak and Virchow, he himself begins to waver in his allegiance to the anti-blastema forces. We shall find also at this time a considerable degree of inconsistency and vagueness in Addison's mode of expression, together with slight but significant changes in his vocabulary. This suggests a falling-off in the quality of his thought or a certain

degree of uneasiness with the scientific stance he had taken at the beginning of his career. The old ideas may be still present, but they have become veiled or softened.

The first of Addison's publications in the eighteen fifties was a series of three papers entitled 'On the containing texture of the blood', published in the *London Medical Gazette*.[4] The phrase 'containing texture'—or 'containing tissue', as Addison sometimes writes—refers to the coats or walls of the blood-vessels. These vessels, he says, constitute a 'sort of frame-work, in the interstices of which are deposited the various substances by which individual organs are characterized'.[5] The walls of the blood-vessels are formed by the blood itself, that is by its fluid and corpuscular elements. 'Blood forms its own containing texture,' as Addison puts it. He notes that the change observable in the upper layer of coagulating blood drawn from the veins of patients with inflammatory disease—that is, its metamorphosis into a fibrous tissue in which colourless corpuscles are embedded—is of the same nature as that constituting the 'containing-tissue of the blood, or the coats of the blood-vessels'.[6] In repair of injury, in inflammation, and in that 'debased' form of inflammation termed scrofulous by Addison, a new growth of tissues and blood-vessels occurs. All investigators concur, Addison tells us, in the belief that 'lymph and lymph particles' under the above circumstances are effused from blood-vessels and subsequently transformed into fibrous and osseous structures (in the case of repair of injury) or into the products of inflammation. Degraded forms of lymph and depraved forms of lymph texture are termed pus and tubercle, Addison points out. The 'phenomena of repair by the metamorphosis of lymph, and the phenomena of inflammation are both expressions, as it were, of exaggerated reciprocal action between the blood and its containing texture'.[7]

Addison is intent on showing that there is less conflict than might be thought between his and the usual doctrines. True, he prefers to speak of 'colourless cells and protoplasma' rather than 'lymph and lymph particles'. But this

is merely a change of words, and he seems quite willing to yield the point. As for the 'prevailing doctrine with respect to effusion of lymph and accumulation of lymph particles', Addison now weakens his position so far as to write that he does not presume to 'deny *the possibility* of cell particles being developed in the effused fluid "as in a blastema",' but he still contends that the 'fact has never been proved'.[8] The evidence that lymph particles in the blood accumulate on the inside of irritated vessels is, on the other hand, too strong to be ignored. Addison makes this remark without saying anything whatsoever about the passage of the 'lymph particles', i.e. of the white blood corpuscles, into the tissues. His manner of expression is very evasive. It cannot be an oversight. The most likely explanation is that he wished to say as little as possible at this time about his most controversial claim. 'It is not necessary,' he writes, 'to the prosecution of our present purpose, to determine the question, whether, and to what extent, lymph particles are generated, as in a blastema, in the effused fluid *outside* the vessels; or whether, and to what extent, they accumulate *on the inside* by separation from the blood within. . . .'[9] He carefully leaves the real alternative unposed—which is not whether lymph particles accumulate on the inside of the blood-vessels, but whether they pass out into the tissues *after* having so accumulated. It is enough that cells are seen to surround and invest the coats of blood-vessels under the circumstances described. For this event, says Addison, is the essential phenomenon of inflammation. During the inflammatory process we observe cells—each one of which is a 'whole or individual organism'—gradually displacing the fibrous elements of vascular walls. And once again he tells us that it makes no difference whether the 'accumulation has accrued *outside* the vessels by generation "as in a blastema", or *inside* by deposition from the blood, or partly by the one process and partly by the other'.[10] What is important is that the fibrous vascular walls are supplanted by layers of cells, the process that he has already termed retrograde metamorphosis. It is only when these cells begin to accumulate and

the vessels to lose their adult form that mere hyperaemia gives way to inflammation.[11]

Whether we consider inflammation with regard to its 'benign and physiological aspect' or to its 'morbid aspect as a destructive process', says Addison, there can be no doubt about the central role played by the colourless cells that invest the vessels and subsequently furnish fibrous or osseous tissue (when repair of injury takes place) or pus corpuscles and scrofulous matter (when the inflammation is unhealthy or scrofulous). 'There can be no possible doubt about the appearance or accumulation of cell-forms upon and around blood-vessels,' he states, 'nor, looking to the general history and physiology of cells in every department of animal and vegetable kingdoms, do we think there can be any reasonable question raised as to the lymph particles being, in the examples we are reviewing, the agents which determine the observed changes, which disintegrate and supplant, or *absorb* the fibrous texture in abscess or ulceration.' These colourless cells are subject to 'inherent deteriorating changes, which modify their character as physiological agents'.[12] In other words, if circumstances are propitious repair and healthy inflammation run their benign and helpful course, if not the result is unhealthy or scrofulous inflammation, the latter a 'persistent form of retrograde metamorphosis'.[13]

In the last paragraph we saw that Addison attributed an abnormal absorptive power to the 'lymph particles' or white corpuscles of the blood. A few years later he returns to this idea in the *Cell Therapeutics*. He speaks now of selective absorption, 'the absorption of some things and the exclusion of others', as a common property of cells. At the same time he cites Kölliker as his authority for the statement that something more than osmosis is involved in the absorptive process, for the membranes of cells are porous and capable of taking up one kind of substance and repelling another.[14] Adapting to his purposes the very old idea that the skin lesions in eruptive diseases represent an attempt on the part of the body to throw off harmful matter, Addison says we

have 'strong evidence that the cells of pustules have absorbed and conveyed injurious matter from the blood' to the external surfaces of the body for discharge. The pus cells, in short, carry out a 'physiological or therapeutical function'. In these circumstances pus is said to be 'laudable'. In general, says Addison, when the component elements of pus and granulations perform their required function in the 'separation of sloughs, the expelling foreign matters by the safest channels, the elimination of poisons from the blood, the establishment of new blood-vessels without bleeding, and the repair of solutions of continuity by the metamorphosis of granulations into fibrous texture' their activities are, using the old medical term, laudable.[15] With his newfound vagueness Addison does not express himself, with regard to the cells chiefly engaged in these endeavours, as clearly as we might wish. But it is plain enough that he has assigned to the pus *cells* the functions assigned by traditional medical theory to pus itself. Two comments should be made here. Firstly, Addison does not regard the white cells of the blood as agents capable of active movement from the blood to the tissues. As we shall see in a moment, it is not quite clear how they do reach the tissues. Although active movements on the part of white cells had already been noted by some investigators Addison was not aware of their findings when he wrote the *Cell Therapeutics*.[16] Secondly, Addison was not the first to assign the pus cells the traditional functions of laudable pus.[17]

Although Addison has not changed his mind regarding the adherence and subsequent accumulation of colourless cells on the inner walls of small blood-vessels as an important feature of the inflammatory process, he now includes it as the 'first phenomenon of a new cell-growth in the vascular tissue, the first act of a much more speedy change in the coats of vessels than occurs in natural adult growth'.[18] We are not told whether this growth is brought about by the new formation of cells in a blastema, by the division of pre-existing cells or by both, but it seems fairly clear that more than the mere accumulation of white cells brought by the

circulating blood is (in his opinion) taking place. He speaks rather vaguely of the 'deciduous mode of growth' of pus cells at sites of inflammation and says that it is similar in kind to the 'vital activity which causes leaves to fall in autumn, discharges sloughs from sores, and poisons from the blood'.[19] At another point he states that during retrograde metamorphosis 'the fibrous coat of the vessels becomes the seat of new cell-growth'.[20] We seem to have met with a new and not fully articulated element in Addison's scheme of things. Most interesting, in view of what has gone before, is the description he now offers of capillary walls in vessels of the smallest calibre. The fibrous coat is said to diminish 'until at a last a thin nucleated membrane only is interposed between the parenchyma of the organ and the blood; and in this membrane no interstices or outlets are visible'.[21] Addison implies that his own observations have led him to this conclusion or at least confirmed it, but he seems merely to have given us a standard description of the kind that he had for so long rejected. Again there is an element of vagueness in Addison's remarks on capillaries, and we are left undecided whether he still holds to his earlier view that there are two types of capillary (the fibrous and the cellular) in the adult organism, or whether he now thinks that the cellular type is absent or very uncommon.[22] Formerly he had overcome the difficulty involved in getting objects the size of white corpuscles through intact vascular membranes by adopting the almost discarded belief that capillaries are wall-less channels. Now he admits that membraneous walls are in fact present (in at least some capillaries) but gets around the old difficulty with the claim that a cellular transformation of the fibrous walls takes place. But the precise relationship between the mere accumulation of white corpuscles on the inner walls of irritated or inflamed capillaries and the growth process of which he speaks is left vague. We may suppose that the vagueness is due to Addison's uncertainty about the nature of the growth process. He is no longer so sure as he once was that those embryonal cells, the white corpuscles, insert themselves into the parenchymal

tissues *à la* Doellinger and Dutrochet and subsequently undergo transformation. We have already seen that in 1850 he could no longer deny the possibility that cells were developed in a blastema or exudate effused from blood-vessels. We find him in 1856 writing that inflammation and tubercle formation are marked by the effusion of pus cells, 'or, to use the terms of the new physiology—marked by the *exudation of blastema and the growth of nucleated cells*' (his italics).[23] Addison, we might almost be ready to believe, is doomed always to hold positions that are in the process of being abandoned by the front line of medical investigators—in some instances, we must admit, positions that will be retaken at a later date on the strength of new evidence.

That the body has inherent powers to ward off noxious agencies, to discharge such as have already penetrated it, to control disease and to restore health, is one of the oldest and most fundamental ideas of Western medicine. Once conceived by the authors of the Hippocratic corpus in ancient Greece it was never forgotten thereafter.[24] The existence of a 'natural healing power' (*vis medicatrix naturae*) does not, of course, presuppose that its exercise will always result in a favourable outcome, as Addison knows quite well. When a lymphatic gland in the groin becomes abscessed following an ulceration of the foot, for example, he interprets this to mean that 'a poison, entering the circulation by absorbent *vessels*, is arrested and discharged by the *cells* of the gland in the thigh'. An indiscriminate absorption by vessels is thus 'rectified by the *discriminate* activity—the metabolic processes—of cells'. And, this being so, 'a basis seems laid for arguing the therapeutical *intent*, if not always the therapeutical *result*, of purulent cell-growth in such cases'. He then ties in his idea of cell therapeutics with the old tradition, for 'what is called the *vis medicatrix naturae* would seem to be referable to the properties of a nucleated cell growth'. Addison believes that it would be to take 'a very partial view of the salutary operations of Nature' were we to limit such operations to a narrowly conceived medical context.

He asks that cell therapeutics be understood in a 'broad physiological sense', including under this heading the formation of new blood-vessels, the healing of solutions of continuity in the solid parts, the sloughing off of dead and useless parts, and so on.[26]

In assessing Addison's ideas at this stage of his career it is well to recall that one of the men he quotes most often is John Hunter, the great eighteenth-century English experimental pathologist and surgeon. There is little doubt that Addison derived from Hunter the idea of regarding inflammation not as a disease, but as a salutary reaction to injury. Addison's phrase, 'salutary operations of Nature', used in the *Cell Therapeutics*, harks back to Sydenham in the seventeenth century and Hunter in the eighteenth. Sydenham's insistence that fever is on the whole a beneficial response of the power of the body to deal with its own ailments is matched by Hunter's claim that inflammation is not a disease, but a 'salutary operation consequent on some violence or some disease'.[26] Hunter was responsible also for including under the rubric of inflammation reparative processes such as the healing of wounds and fractures. His ideas on the nature of inflammation were influential but they were by no means universally adopted. The rival view that fever and inflammation were in themselves harmful and therefore to be combated by the physician was probably held by the majority of physicians in England during Addison's lifetime. And on the European continent, especially in Germany, there was a strong anti-teleological sentiment among scientifically oriented physicians that made them reluctant to accept the implied purpose of 'reactions' on the part of the body. This should be borne in mind when we find Addison stating that 'neither heat nor cold, nor poisonous air, occasion inflammation directly'; what they do occasion, he says, is 'injury to the solid parts or the blood, and from injury arises inflammation . . . reaction, in all of these cases, is denoted by some form of inflammation'. The same considerations applied to fever.[27] Inflammation, then is reaction to injury, a definition that would fit neatly into

modern (1970) textbooks of pathology. But Addison, as usual, was either too late or too early (depending on the direction in which we turn our historical vision) in his attempt to bring some of Hunter's ideas on inflammation and repair into the context of a cellular physiology, pathology and therapy.[28]

Bibliography and Notes

1. Addison, *On Healthy and Diseased Structure*, op. cit., p. 226; *Cell Therapeutics*, London, 1856.
2. Ibid., pp. vii–viii.
3. Cf. Ch. II.2, note 30; II.3, note 25.
4. William Addison, 'On the containing texture of the blood', *Lond. med. Gaz.*, 1850, **46**, 193–98, 316–21, 488–83.
5. Addison, op. cit., p. 195.
6. Ibid., p. 196.
7. Ibid., pp. 197–98.
8. Ibid., p. 316.
9. Ibid.
10. Ibid., p. 318.
11. Ibid., p. 319.
12. Ibid., p. 490.
13. Ibid., p. 493.
14. *Cell Therapeutics*, op. cit., pp. 12–18.
15. Ibid., pp. 24–27. Addison quotes on page 24 the following passage from Sydenham: 'An epidemical disease must be regarded as an effort of nature to restore the health of the patient, by the elimination of the morbific matter, which would otherwise undo the fabric of the body. During febrile ebullition the elements which fret the blood are picked out, gathered together, and made over to the fleshy parts of the body for expulsion.'
16. This follows from a statement on page 27 of *Cell Therapeutics*, where Addison remarks that the cells of different kinds of pus cannot be distinguished under the microscope. The reason is that 'different species of animal cells, unless deeply coloured, are very much like to one another, and some kinds of animalcules which live in decomposing animal and vegetable infusions, would be scarcely distinguishable from pus cells, were it not for their varied and spontaneous movements'.
17. It would appear that the pus cells were assigned this function by at least some theorists not long after they were recognized as distinct microscopic entities. At any rate we find Virchow, as early as 1847, calling the view outmoded. With a critical eye toward all teleology in pathology, he

wrote that 'suppuration is no longer a therapeutic effort of the organism to fill this or that breach, the pus corpuscles are no longer the gendarmes ordered by the police state to escort some stranger or other without a passport over the border; scar-tissue no longer constitutes the prison walls within which this stranger is enclosed, when the police-organism so pleases' (*Ueber die Reform*, op. cit., p. 216).

18. *Cell Therapeutics*, op. cit., p. 30.
19. Ibid., p. 32.
20. Ibid.
21. Ibid., pp. 39–40.
22. Ibid., p. 41.
23. Ibid., p. 45.
24. On the subject in general see Max Neuburger's *Die Lehre von der Heilkraft der Natur im Wandel der Zeiten*, Stuttgart, 1926; English trans. by Linn J. Boyd, New York, 1932.
25. *Cell Therapeutics*, op. cit., pp. 28, 29.
26. John Hunter, *A Treatise on Blood, Inflammation and Gun-Shot Wounds*, ed. with notes by James F. Palmer, Philadelphia, 1840, p. 285. Early in the eighteenth century Georg Ernst Stahl held—in opposition to most scientifically oriented physicians of his time—that the inflammatory process was essentially an attempt on part of the governing powers of the body to overcome blockage or stasis in the smallest blood-vessels. The physician, wrote Stahl, should let his patient know that the discomfort brought by inflammation was much to be preferred to the consequences that would result were inflammation to remain absent (*Theoria Medica Vera*, ed. Ludwig Choulant, 3 vols., Leipzig, 1831–33, vol. 2, pp. 220–23). The phrase 'salutary act' (*actus salutarius*) was first used in relation to the inflammatory process by Stahl's pupil and successor in the chair of medicine at Halle, Michael Alberti.
27. *Cell Therapeutics*, op. cit., p. 52.
28. Addison's book seems to have attracted little attention. An unsigned review in the *Lancet*, 26 April 1856, p. 461, briefly called it 'an attempt, according to the author, to consider the phenomena of cure and reparation in connexion with the cell physiology' and cited a few short passages without further comment. An unsigned review in the *Medical Times and Gazette* characterized it as a book 'worthy of the high reputation of the author', but had nothing else to add.

III.3 Addison's Gulstonian Lectures (1859)

The White Cells Diminish in Importance

Three years after the publication of his *Cell Therapeutics* Addison, in the capacity of Gulstonian Lecturer, gave a series of talks on fever and inflammation in London before the Royal College of Physicians. The lectures were published in the *British Medical Journal* in the same year.[1] We find him, as before, stressing his essentially Hunterian view that the 'forms of inflammation, granulation, pus, suppuration, and ulceration, are ordinary phenomena of therapeutical reaction in injuries and disease . . . protraction or chronicity, or even danger to life from physical hindrances, does not impugn, or exclude the conception of a process established for reparation, though it should fail'.[2] But several new features are present in his account of the mechanism of the body's resistance to harmful agencies. Also, his new conception of the development and nature of capillary walls is stated in a manner less equivocal than heretofore. As for the white corpuscles of the blood, we shall see that their place in Addison's scheme of things has further decreased in importance. One of their old functions has been assigned to the red corpuscles. In addition, Addison has come to believe that the *red* corpuscles play an important part in the reaction of the body to inhaled 'miasms' of contagious diseases, such as smallpox, scarlet fever and diphtheria. Reading these papers can be a somewhat confusing affair.

The modern reader—especially one with some knowledge of pathology—who has followed the apparent direction of Addison's thought (and at the same time had in the back of his mind the course actually taken by pathology after Addison's death) is apt to have a strong feeling that when Addison refers simply to 'corpuscles' he ought to be referring to the white corpuscles, when he is in fact referring to the red. Addison's new ideas, it should be stated, are only loosely attached to an empirical base and are unsupported by

any but a somewhat crude repetition of one of his earlier demonstrations.

The first of the new elements in Addison's thought is an emphasis on the 'common tissue'—the connective tissues throughout the body, in modern terms—as the primary locus of the inflammatory process. Echoing the majority opinion of his time, Addison states that the common tissue is diffused throughout the developing embryo and 'at first composed of cells and nuclei'. As development proceeds the cells of the common tissue are transformed into fibres. When 'growth has been completed nuclei are found incorporated with the fibres in fibrous membranes, in the coats of the blood-vessels, in capillaries . . .' and in the remaining common tissues.[3] The idea that the inflammatory process is one essentially involving the connective tissues, rather than the nerves, blood-vessels or parenchymal cells (to name the three chief contending sites) is interesting and important, but Addison, unfortunately, does not develop it further. Taken together with his now fairly thorough disposal of wall-less capillary channels, however, it helps us to understand why we hear no more from him regarding the interrelationships of inflammatory and nutritive processes. For if all or almost all of the capillaries in healthy adult tissues have complete fibro-membraneous walls it is hard to see how white corpuscles could pass out of the bloodstream to become intercalated in the tissues as part of the normal nutritive process, which is what Addison once held. It is only during the inflammatory process, when the capillary walls undergo cellular transformation or 'retrograde metamorphosis', that white cells can conceivably pass out into the tissues. And even in this connexion we must not forget that Addison has acquired the habit of avoiding all mention of the outward passage of colourless cells from the blood to the tissues. He still seems to regard the white cells as embryonal in some sense, for he describes the embryo as a 'microscopical mass of colourless cells' and observes that foetal and maternal blood 'abounds in colourless elements'. And he still connects the white cells in some unspecified way with

the nutritive process, as we see when we read that their increased number in foetal and maternal blood and in blood drawn from vessels near the 'sphere of action' of inflammation and repair leads him to infer that 'the plasma or colourless elements of the blood furnish material for the growth of the common tissue'. The statement, it should be noted, says only that the growth of common tissue is thus provided for, and is phrased so as to be compatible with blastema theory.[4]

Addison now surprises us by espousing, for the moment at least, Carl von Rokitansky's rather idiosyncratic humoralistic doctrine asserting the presence of chemical alterations in the proteins of the circulating blastema that determine the character of certain pathological–anatomical changes seen in disease. We could perhaps have wished that Addison, instead of moving from tolerance to tacit acceptance of blastema theory, might rather have attached himself to the Virchowian assertion that all cells arise from other cells. Due to factors that have been touched on in passing, this had no doubt become an increasingly unlikely event, but it is tempting to wonder what the effect on Addison would have been had the English translation of Virchow's book on cellular pathology appeared in 1858 instead of 1860. Putting the temptation aside we turn to some features of Rokitansky's book that appealed to Addison. He had at his disposal the English translation of 1854 of the German original published in 1846. Unlike others who had adopted the blastema theory in their efforts to explain pathological anatomical changes Rokitansky did not take the circulating blastema as a constant, so to speak, and attempt to locate the variables in the tissues. Instead, he proceeded on the assumption of 'primitive diversity' of blastemas in the circulating blood. Various abnormalities of the proteins constituting the circulating blastema were, in his opinion, responsible for the peculiar character of local pathological anatomical changes following upon exudation. For example, a 'cancerous dyscrasia', brought about by the appropriate chemical change in the circulating proteins of

the blastema would result after exudation in the local development of a malignant tumour.[5] In referring his audience to that '*chef d'œuvre* of pathological anatomy', the great work of Rokitansky, for evidence that 'forms of inflammation depend on distemperatures or dyscrasies of the fluid of the blood',[6] Addison, ironically enough, does so in all innocence of the fact that Rokitansky himself, partly in response to Virchow's biting criticism in 1846 of his book, had in 1855 issued a revised version in which all traces of the primary diversity of blastemas had vanished.[7] But we need not concern ourselves too deeply with Addison's espousal of Rokitansky's views for it seems little more than an attempt to lend respectability to a new idea of his own.

The new idea has to do with the activities of the red corpuscles in coping with the inhaled 'miasms' or 'viruses' that Addison considered were the causative agencies of contagious diseases. Addison, together with many of his colleagues shared the belief that living agents of some kind were concerned in the causation and spread of contagious diseases. (He has little to say on the subject, aside from his rejection of the view expressed by Liebig and the chemical school that the agencies were chemical rather than biotic.) The red blood corpuscles are, Addison states, 'independent organisms, swimming in the plasma' and, like the 'unicellular animalcules' that they so closely resemble, dependent for their nourishment on substances present in the surrounding fluid. They take up these substances from the plasma and discharge their wastes into it as well. This waste material, in turn, has to be discharged in some manner from the circulating blood, else the organism as a whole would be poisoned by its accumulation. For this purpose the organism has at its disposal certain 'depurating organs' (the most important of which are the lungs and the kidneys) that withdraw harmful matter from the plasma and discharge it externally. Thus 'carbonic acid is an excretion discharged into the plasma, and withdrawn therefrom by the action of the kidneys'.[8]

Now, continues Addison, in disease the plasma or fluid

elements of the blood may become disordered as a result of dietary errors. If the disorder is severe enough the red corpuscles may be adversely affected in respect to their activities. But when a 'miasm' (a poisonous substance in the atmosphere) is taken in through the lungs the red corpuscles, by virtue of their respiratory function, are primarily affected and the plasma, if at all, secondarily. According to Addison, the red cells, like all cells in the body, have an inherent ability to resist the action of injurious agencies. The red corpuscles of the blood 'infected with a contagious poison, therefore react against it; they excrete, throw off, or free themselves from the virus. . . . The prosecution of the virus then devolves on the plasma; and in small-pox, inflammation and pustulation in the common tissue of the skin is established for its final expulsion and the patient's recovery.' Where the 'virus' of smallpox, i.e. the miasm or poisonous substance or agent assumed to be the cause of the disease, is concerned, Addison deems the 'physiological demand . . . analogous to that where abscess and ulceration is established for the expulsion of a thorn or sloughs'. This is, a thorn gives rise to a physiological demand for its expulsion from the solid tissues, whereas in 'small-pox and other fevers, the demand is for the expulsion of some hurtful matter from the plasma of the blood'. In both cases, he adds, inflammation is the organism's reply to the demand.[9] Inflammation, including suppuration, is thus a kind of *ad hoc* depurating process.

Now what, in Addison's opinion, is the role of the white corpuscles of the blood in this reactive process? Are they the gendarmes who seize unwanted visitors unprovided with passports and escort them to the border?[10] Addison does not tell us. All he has to say is this: 'When abnormal qualities of the plasma promote inflammation . . . the disposition of colourless corpuscles of the blood to congregate and attach themselves to the coats of the vessels, we may suppose to indicate a way whereby disqualified or abnormal portions of the plasma are transferred to the common tissue for discharge.'[11] As before he does not refer to their pas-

sage out of the bloodstream. And in the blood itself the red corpuscles, rather than the white, 'in their reactions upon extraneous substances . . . throw off matter into the fluid in which they swim'.[12]

Bibliography and Notes

1. William Addison, 'Gulstonian Lectures on Fever and Inflammation', *Brit. med. J.*, 1859, 23 April, pp. 332–35; 30 April, pp. 352–54; 7 May, pp. 367–69; 14 May, pp. 386–88; 21 May, pp. 404–6; 28 May, pp. 424–26; 4 June, pp. 445–47; 11 June, pp. 463–65.
2. Ibid., pp. 334–35.
3. Ibid., p. 332. Addison presents here the usual view that the connective tissues are acellular in structure in adult life.
4. Ibid., p. 333. Addison is so ambiguous here that we cannot be quite certain just what he does mean. Is the 'or' in the phrase 'plasma or colourless elements of the blood' disjunctive, offering his auditors a choice between blastema and corpuscular theory? Apparently not, for it seems to have been Addison's intent to assimilate the two. He lists the constituents of plasma as 'water, fibrine, albumen, colourless corpuscles, volatile matter, fatty compounds and salts', and then adds that in its passage through the capillary vessels the plasma permeates all organs and tissues (ibid., p. 352). Is this standard blastema theory or does Addison mean that the colourless corpuscles pass out as part of the plasma?
5. Carl von Rokitansky, *Handbuch der allgemeinen pathologischen Anatomie*, Vienna, 1846; Eng. trans. by W. E. Swaine, *A Manual of General Pathological Anatomy*, London, 1854.
6. Addison, op. cit., p. 353.
7. Carl von Rokitansky, *Lehrbuch der pathologischen Anatomie*, 3rd ed., vol. 1, London, 1855. This work was never translated into English. For the text of Virchow's critical remarks on the *Handbuch* see L. J. Rather, 'Virchow's review of Rokitansky's *Handbuch* in the *Preussiche Medicinal-Zeitung*, December 1846', *Clio Medica*, 1969, 4, 127–40.
8. Addison, op. cit., pp. 353, 54, 67.
9. Ibid.
10. Cf. Ch. III.3, note 17.
11. Ibid., p. 353.
12. Ibid., p. 405. In connexion with diphtheria and scarlet fever, Addison states that he formerly 'supposed the free molecules, observed in the plasma of blood, drawn in cases of fever and inflammation, to be derived from the colourless corpuscles', but now has learned that they are thrown out by red corpuscles. When a drop of blood was mixed with a drop of sherry wine the red corpuscles could be seen to 'throw out molecules around their circumference', the same molecules, Addison adds, that he

first described in 1841–42 in the blood drawn from patients with inflammatory diseases.

III.4 The 'Amoeboid' Behaviour of Cells in the Blood and Tissues

Cohnheim's description of White Cell Migration through Vascular Walls (1867)

We know that Addison was aware, at least as early as 1856, of the visual resemblances between certain minute free-living organisms, such as amoebae, and cells (in particular the colourless corpuscles of the blood) that were parts of larger organisms, although he was unaware that the movements displayed by free-living cells were matched by those of cells in the blood and tissues.[1] The case for the identity of white blood cells, pus cells and mucus corpuscles, which he upheld, was to be strengthened in the early eighteen sixties by the addition of a similarity in behaviour, i.e. the presence in all three of movements called 'amoeboid', to the already well-recognized similarities in appearance. An additional point of resemblance between the mobile cells of larger organisms and free-living animalcules, recognized at about the same time, was the ability of both to engulf bits of particulate matter in the surrounding fluid. Investigators were soon to take advantage of this ability for the purpose of labelling or tagging the cells in question with particulate dyes. In this way their peregrinations through the tissues could be readily followed.

As far as cells in animal organisms were concerned, movements of the type here referred to were at first subsumed under the general heading of 'contractility', in the same category that included the contraction of muscle cells and the movement of cilia. Change of contour rather than progressive movement of the cell as a whole was emphasized.

Wharton Jones described in 1846, probably for the first time, 'remarkable changes of shape' in coarsely and finely granulated colourless cells in the blood of frogs and skates. He saw coarsely granulated frog white cells 'in blood drawn from the living animal, exhibiting changes of shape with movements of the granules'. And in human blood he had seen coarsely and finely granulated cells 'shooting out processes like the same cells in the blood of the frog'.[2] In France similar observations were made in 1850 by Davaine on white cells in blood drawn from both frogs and men. He described as many as 'twenty changes of form' in the space of half an hour, and expressed the view that white cells adherent to the inner walls of irritated small blood-vessels likewise underwent changes of form analogous to those which they 'manifest in a drop of blood placed on a glass slide'. The movements, he wrote, resembled those of 'certain infusorial animals, proteans or amoebae, for example'.[3] And in Germany in 1854 Lieberkühn, seemingly unaware of Wharton Jones' and Davaine's publications, described the amoeboid (*amoebigartigen*) movements of frog white blood cells in the following words: '. . . a spherical body gradually stretches forth a process, draws it back again, stretches out a new one at an entirely different point, draws this once back also. . .'.[4] Addison could also have read a note by Busk and Huxley in 1853 commenting on the contractile movements shown by various protozoa and algae and calling attention to 'distinct protean movements, like those of the colourless corpuscle', on the part of mucus corpuscles.[5] All these publications appear to have escaped his attention.

The movements described by Wharton Jones, Davaine, Busk and Huxley, and Lieberkühn were contractile rather than locomotive. In 1863, however, Friedrich von Recklinghausen described locomotive movements in pus corpuscles and in certain connective tissue cells.[6] Such cells, he wrote, 'wander, as a consequence of their changes of form'.[7] In the space of half an hour, in fact, they might traverse an entire microscopic field.[8] In order for movements on the part of pus corpuscles to occur it was necessary,

von Recklinghausen found, to avoid the use of any but the thinnest of glass coverslips. Preferably the cells should be observed in thin uncovered fluid films. Such films were of course subject to rapid evaporation. To avoid this difficulty von Recklinghausen devised a moist chamber attachment for his microscope, a simple cuff containing a moistened wick, the whole sealed above to the microscope objective and below, by an oil ring, to the glass slide bearing the fluid film of diluted pus. Von Recklinghausen considered that the work of earlier investigators had established the identity of the movements seen in colourless blood and lymph corpuscles.[9] His own findings, he claimed, demonstrated for the first time that movements falling into the same category were displayed by pus corpuscles. Pointing out that Virchow had always insisted on the morphological identity of white blood cells and pus corpuscles, von Recklinghausen stated that it was now justifiable to assume the 'complete identity of both structures'. Furthermore, in accordance with the findings of Busk and Huxley, mucus corpuscles could be included in the group.[10]

Von Recklinghausen had earned his medical degree at Berlin in 1855 with a thesis on the subject of pyaemia. From 1858 to 1864 he worked as an assistant at Virchow's institute of pathology in Berlin. He was of course aware that Virchow's cellular pathology ascribed the origin of pus corpuscles to two sources only, to the epithelial cells of mucous membranes and the connective tissue cells.[11] Along with almost every other physiologist and pathologist Virchow had rejected the seemingly quite outmoded belief that pus corpuscles represented extravasated blood corpuscles. But the findings of von Recklinghausen would seem to cast some doubt on Virchow's by now standard account of the origin of pus corpuscles at inflammatory sites. Von Recklinghausen himself pointed out that since pus corpuscles had been shown to be capable of traversing relatively large stretches of tissue it followed that their accumulation at any given point did not necessarily mean that they had arisen there. He suggested that their power

of movement might allow them to reach the surface, of ulcers to pass through open channels or passages in the body, to accumulate in the body cavities and to move through the connective tissues to the surfaces of mucus membranes.[12] Just where it was that they first took origin was a question to which he offered no answer, stating only that he had been unable to find evidence that they arose by division of cells in the connective tissues.[13]

Von Recklinghausen was apparently more interested in where the 'wandering' cells went than in where they originated. In order to pursue further his studies along this line he made use of their by then well-known ability to engulf finely particulate dyes. It had, he noted, long been known that amoebae exhibited this behaviour and it had been shown by Ernst Haeckel as well that the colourless blood cells of lower animals could take up particles of carmine.[14] For his own purposes von Recklinghausen introduced finely particulate vermilion along with bits of corneal tissue into the subcutaneous lymph sacs of frogs. The corneal tissue (which was chosen partly because of its lack of blood-vessels) was taken from dogs, rabbits or the test animal itself. After a few days von Recklinghausen was able to detect cells containing particles of the dye within the corneal substance. Since the bits of corneal tissue were as much as fourteen days old in some of his experiments it seemed unlikely to him that any of the original stellate corneal cells (normally present in the tissue) could have survived. The tagged, vermilion-bearing cells were, therefore, 'wandering' cells from the lymph of the test animal. By virtue of their contractile powers they must have taken up particles of the dye and then migrated, probably along blood or lymph channels, into the corneal tissue.

The choice of corneal substance as a test object by von Recklinghausen reflected the widespread interest of pathologists in the inflammatory process as it took place in this easily visible and available avascular tissue. When the cornea of a living animal underwent inflammation, say by the application of silver nitrate to its surface, the earliest visible

change was a loss of the normal translucency. Under the microscope this was revealed to be in part the result of an accumulation of new 'inflammatory' cells. Virchow and his school ascribed the new cells to an enlargement and subsequent multiplication of the normally present stellate corneal corpuscles.[16] The reader may perhaps wonder why von Recklinghausen, after having shown that colourless lymph corpuscles tagged with vermilion dye migrated into bits of corneal tissue suspended in the lymph sacs of frogs, after having identified lymph, pus and white blood corpuscles on grounds of both appearance and behaviour, and after having expressed doubts as to the origin of pus corpuscles at inflammatory sites, did not take the obvious next step, namely, to tag the amoeboid cells of blood and lymph and then induce corneal inflammation in the same animal. If the tagged cells then made their way to the inflamed corneal tissue, the obvious inference could have been drawn. (Von Recklinghausen, incidentally, had already found that some of the vermilion particles injected into the subcutaneous lymph sacs of the frog could be found later in white blood corpuscles.) Perhaps the step was not as obvious as it appears in retrospect. Or von Recklinghausen may have felt that he had already come close to treading on the toes of his master. In any case his chief interest lay not in the subject of inflammation but in the existence in the tissues and fluids of animal bodies, up and down the scale of life, of a widely distributed group of cells sharing the common property of mobility, the 'wandering' cells, as they came to be called.[17]

Four years later in 1867 another of Virchow's assistants, Julius Cohnheim, took the step before which von Recklinghausen had hesitated.[18] Working also with the cornea Cohnheim found that a gold chloride staining procedure of his devising imparted a reddish-violet colour to the original corneal corpuscles as well as to the new cells appearing in the course of inflammation. In still living inflamed corneal tissue examined under the microscope the normally present corneal cells could readily be distinguished from 'colourless,

uninucleate or multinucleate cells resembling lymph corpuscles or, to use a more convenient expression, pus corpuscles'. The former were fixed in place, while the pus cells wandered through the tissues; their contours were relatively stable, while the pus cells took on all manner of bizarre forms.[19] Use of the gold chloride staining procedure involved the death and cessation of movement of all cells present in the cornea, but Cohnheim found that the two cell types could still readily be distinguished. The fixed corpuscles stained more lightly than the new cells. Further, the new inflammatory cells contained two or more small nuclei instead of the single large nucleus characteristic of the fixed corpuscles. A careful study of thin sections made from inflamed corneas convinced Cohnheim that during inflammation the fixed corpuscles underwent no changes in number or position. Some other source for the new cells had to be found.[20]

In Cohnheim's opinion, 'either the pus corpuscles arose from pre-existing, wandering lymph corpusculoid elements in the cornea, or they arose not from the cornea at all, but from outside; they wandered in'.[21] Using frogs and following von Recklinghausen's procedure he then injected colloidal aniline blue into (a) the space between the cornea and the nictitating membrane, (b) the anterior chamber of the eye and (c) the subcutaneous lymph sacs. In each instance he followed up the injection of dye with the induction of corneal inflammation. Only in case (c) did pus cells containing blue granules make their appearance in the inflamed corneas. By repeatedly injecting dye into the lymph sacs of frogs he was able to raise the proportion of tagged cells to as high as 10 per cent of the total. The inescapable conclusion was that particles of dye had been taken up by amoeboid wandering cells in the lymph, some of which had then migrated to the cornea. Next he injected dye into the bloodstream of frogs, induced inflammation of the cornea as before and within a few days found cells bearing the blue granules present in the corneal substance.[22] Accordingly, 'some pus corpuscles in the inflamed cornea were formerly

colourless blood corpuscles; they forced their way into the cornea from the blood-vessels'.[23]

Repetition of these experiments in a warm-blood animal, the rabbit, uniformly ended in failure. Cohnheim found that the particles of dye were immediately and completely taken up by cells lining the small blood-vessels of the liver before they could be ingested in sufficient number by cells in the circulating blood.[24] He then turned to that once very familiar object of microscopical study, the mesentery of the frog small bowel. His procedure was to immobilize the animal with the newly available drug curare, draw out the small intestine through a small incision in the abdomen, and examine the mesenteric membrane under the microscope.[25] Small veins, he found, could easily be distinguished from small arteries, since only the latter pulsated. He re-described the phenomenon of axial streaming, pointing out that immediately after exposure of the mesenteric vessels an almost cell-free zone of plasma was present between the vessel wall and the central axis of hurrying red and white corpuscles. In the space of two or three minutes one could see white cells becoming detached from the central axis, appearing momentarily in the relatively slow-moving peripheral plasma stream, bumping against the vessel wall and perhaps briefly remaining in contact with it. The axial stream was broader in the veins than in arteries of corresponding size, and absent altogether in capillaries (by the latter Cohnheim understood tiny vessels at most capable of carrying two blood cells side by side).[26]

To excite inflammation in the mesenteric tissues Cohnheim at first used cotton or cantharides as irritants, but he soon found that mere exposure to the air sufficed. Within fifteen to thirty-six hours after exposure the mesentery and surface of the intestine alike were covered with a yellowish or grey sticky layer of typical fibrino-purulent exudate consisting largely of pus corpuscles, together with a few red corpuscles and intermingled granular matter. Cohnheim's description of the microscopically visible events leading to the formation of this exudate is admirably clear, although

much of it of course merely recapitulates what had been described many times before. Within ten to fifteen minutes, he writes, the arteries dilate to about twice their original diameter. The veins follow more slowly while the capillaries dilate little if at all, although they become more prominent due to an increased number of passing cells. As the dilatation proceeds the flow of blood within arteries and veins slows, the stream loses its axial character and the peripheral plasma layer slowly fills with colourless cells. Within a few hours the walls of the small *veins*—not those of arteries or capillaries—are seen to be tapestried by an unbroken layer of adherent white blood corpuscles. Meanwhile, the red blood cells flow by undisturbed.[27] The observing eye, says Cohnheim, is then 'arrested by a very unexpected event' in the walls of the veins. In his own words: 'small, single, colourless, knob-like protrusions appear on the outer contour of the vein wall, as if the vascular wall itself were sprouting knobby outgrowths. These outgrowths slowly and very gradually become larger; after a time a hemisphere about half the size of a white blood corpuscle appears on the outside of the vessel and then the hemisphere changes into a pear-shaped structure with its swollen end turned away from the vessel and the pointed end planted in its wall. From the periphery of the pear-shaped body fine extensions and scallops now begin to radiate outward, and the entire contour, hitherto one more or less rounded, takes on extremely variegated forms. In particular, however, the main mass of the body, the swollen and now scalloped end, removes itself further and further from the vascular wall, while the pointed end is gradually drawn out into a fine, increasingly extended stalk that I have seen reach 0·05, even 0·07 millimetres in length. But at last this stalk separates from the point on the wall where it has so far been firmly seated, and we now have before us a colourless, rather glittering, contractile body with several short and one very long projections, the size of which completely corresponds to that of a white blood corpuscle, and in which one or more nuclei are visible, not uncommonly in the fresh state after a few changes of shape and

in any case after treatment with reagents, consequently a body that is in no way different from a colourless blood corpuscle itself.'[28]

The timing of the whole process was highly variable, Cohnheim pointed out, and such as to hide the crucial event from the eye of all but the most persistent observer. Several hours might elapse before the 'tapestry' of colourless cells formed on the interior venous wall. The passage of a single white cell through the wall might require as much as three hours. Often passage took place intermittently and irregularly along the course of a given vein, anywhere from its smallest branches up to a main trunk. He had watched for as long as fifteen hours without seeing a single cell emerge from one stretch of vessel wall while in an adjacent stretch they were passing through in relatively lively fashion. But when the nature of the event had been grasped its various states could readily be observed in cells scattered along the course of vessels. Cohnheim, we saw, found that passage of white cells occurred predominantly through the walls of small veins. He called the event 'an emerging of colourless blood corpuscles from the interior of a vein to the outside, completely through the intact vascular wall'.[29] (We shall see that at a later date he changed his mind with respect to both the supposed intactness of the wall and the importance of active amoeboid movements on part of the escaping cells.) The migration of white cells through the walls of the true capillaries (vessels small enough to allow the passage of only one or two cells at a time) was far less common but it did occur. 'The first to be observed at such sites,' writes Cohnheim, 'is that the formerly spherical colourless blood corpuscles exhibit changes of form that can be of variable rapidity and extent but always display the well-known character of amoeboid movements . . . where a white corpuscle lies within the capillary one sees on the outer surface of the vessel wall a hump-like elevation or perhaps a fine, spine-like outgrowth that gradually grows larger and larger and finally, just as in the veins, is transformed into a colourless corpuscle connected to the capillary wall only by a long

drawnout stalk, so as in the further course of events to free itself completely from that point.'[30] It was Cohnheim's opinion that amoeboid white corpuscles passed through the points of junction of the endothelial cells that were joined together in mosaic fashion to form the vessel walls. This took place by virtue of a 'pushing forward of their processes against those points of the vessel wall where no resistance, or the least, meets them, and these are the stomata'.[31] It was at about this point in his paper that Cohnheim called attention to the 'exact and true observation' of these same events by William Addison in 1849.[32]

Bibliography and Notes

1. Cf. Ch. III.2, note 16.
2. T. Wharton Jones, 'The blood-corpuscle considered in its different phases of development in the animal series', *Phil. Trans. R. Soc. Lond.*, 1846, pt. 1, pp. 63–87.
3. Casimir J. Davaine, 'Recherches sur les globules blancs du sang', *C. r. Séanc. Mém. Soc. Biol., Paris*, 1850, **ii**, 103–5 (Paris, 1851). Davaine was apparently unaware of Wharton Jones' observations.
4. Johann Nathaniel Lieberkühn, 'Ueber die Psorospermien', *Arch. Anat., Physiol. wiss. Med.*, 1854, pp. 1–24. According to Lieberkühn movements of this kind were described in the lymph corpuscles of frogs by Nasse and Müller. Karl Rothschuh's *Entwicklungsgeschichte physiologischer Probleme in Tabellenform* (Munich, 1952) states on p. 9 that Wharton Jones 'discovered the ameboid movements of leucocytes' in 1842, but I cannot find any such description in the article to which reference is made (*Brit. for. med. Rev.*, 1842, **14**, 585–60. Strictly speaking, what Wharton Jones described in 1846 were movements of a kind later to be compared by other observers (of whom Davaine was apparently the first) to the movements of amoebae.
5. R. A. von Kölliker, *Manual of Human Histology*, trans. and ed. by George Busk and Thomas Huxley, London, 1853, 2 vols., vol. 1, p. 46.
6. Friedrich von Recklinghausen, 'Ueber Eiter- und Bindegewebeskoerperchen', *Arch. path. Anat. Physiol. klin. Med.*, 1863, **28**, 157–97.
7. Ibid., p. 170. Although von Recklinghausen uses the term 'wandering' (*wandernde*) to describe the movements of these cells, he does not suggest it as an appropriate name. He tells of a description by Kölliker of such movements in cells of sea-squirts, for which a young friend of Kölliker has suggested the name 'strolling cells' (*spazierende Zellen*). Kölliker himself regarded the designation as more fanciful than real (loc. cit.,

p. 189). We may recall here that Dutrochet spoke of *cellules vagabondes* in his paper of 1824 (later disclaimed). Dutrochet, however, said nothing of active movements on part of the cells in question (cf. Ch. II, notes 6, 7).

8. Ibid., p. 171.
9. Ibid., p. 163.
10. Ibid., p. 187.
11. For Virchow's views on the origin of pus cells (after he had given up the blastema theory) see *Die Cellularpathologie*, 1st ed., op. cit., pp. 353–61.
12. Recklinghausen, loc. cit., p. 190.
13. Ibid., p. 192.
14. Ibid., pp. 163, 184. He cites Ernst Haeckel's monograph on *Radiolaria*, Leipzig, 1862, p. 104.
15. Ibid., pp. 185, 186. In the same issue of the *Archiv*, pp. 237–40, Virchow contributed a brief paper entitled 'Ueber bewegliche thierische Zellen' in which he supplemented the work of von Recklinghausen with some observations of his own on mobile cells found in the fluid of hydroceles.
16. Cf. Virchow's *Die Cellularpathologie*, 1st ed., op. cit., pp. 271–75. The earliest stage of the opacity was due to enlargement and granularity of the original corneal corpuscles. Virchow's interest in the cornea as the site of what he called 'parenchymatous inflammation', i.e. the inflammatory reaction as manifested by cells *per se*, independent of vascular participation, was of long standing. His first medical paper, published in 1843, was an inaugural dissertation, *De rheumate praesertim corneae*.
17. Wilhelm Preyer offers a good review of the activities of amoeboid cells, with numerous references to the contemporary medical and biological literature (including the work of Ernst Haeckel, Max Schultze, Wilhelm Kuehne, Ernst von Bruecke, Virchow, von Recklinghausen and others) in his 'Ueber amoeboide Blutkoerperchen', *Arch. path. Anat. Physiol. klin. Med.*, 1864, **30**, 417–41. With respect to the uptake of particles by vertebrate and invertebrate amoeboid cells, Preyer states that the nature of the ingested substance is a matter of indifference since 'indigo particles, carmine granules, vermilion dust, milk spherules, etc. are intussuscepted in like manner . . . the extent to which the described kind of uptake of material effects nutrition of the cell cannot yet be estimated, for there are not even probable grounds that the substance taken in (if it should in general be so suited) is assimilated'. Note that he does not mention the uptake of micro-organisms and is uncertain as to the disposal of the ingested material.
18. Julius Cohnheim, 'Ueber Entzuendung und Eiterung', *Arch. path. Anat. Physiol. klin. Med.*, 1867, **40**, 179. As von Recklinghausen had done six years before him, Cohnheim earned his degree at Berlin in 1861 with a thesis on pyaemia.
19. Ibid., pp. 2–4.

20. Ibid., pp. 6–11.
21. Ibid., p. 13.
22. Ibid., pp. 19–22. Cohnheim used von Recklinghausen's procedure for inducing keratitis by touching the surface of the cornea with a silver nitrate stick.
23. Ibid., p. 24. Cohnheim notes on p. 23 that he has 'never seen coloured granules in the very small elements that hardly or only by a very little exceed the red blood corpuscles in size'. But in all other types of white blood cells, especially in the 'larger forms or those characterized by amoeboid movements', whether finely or coarsely granular, he found particles of the dye.
24. Ibid., p. 26.
25. Ibid., p. 28.
26. Ibid., p. 32. Cohnheim says that Weber first called attention to the axial stream, citing his paper of 1837. Cf. Ch. I.4, notes 10–12.
27. Ibid., pp. 33–47.
28. Ibid., pp. 38, 39. If Cohnheim's description is compared with Waller's (Ch. II.4) it will be seen that what Cohnheim took to be the body of the escaping white cell was regarded by Waller as a protrusion of the vessel wall.
29. Ibid., p. 41.
30. Ibid., p. 44.
31. Ibid., p. 55. The 'stomata' were concentrations of cement substance at the junctions of endothelial lining cells, demonstrated by von Recklinghausen's silver impregnation technique and interpreted as small openings or pores in the vascular wall.
32. Ibid., pp. 57, 58. He was unaware of Addison's earlier work.

III.5 Reception and Further Development of Cohnheim's Findings

Addison's last work: *The Co-Existence of Two Species of Inflammation* (1868)

The climax of our chief theme has now been reached. Addison's hypothesis of 1844 has been experimentally verified by Cohnheim twenty-three years later. It was soon to be almost universally accepted as fact by pathologists and thereafter transmitted as received doctrine to succeeding

generations of physicians. True, Waller had at least partially verified Addison's hypothesis as early as 1846. But we have not found a single reference in the literature to Waller's papers between the time of their publication and the appearance of Cohnheim's paper in 1867. On the other hand the early papers of Addison, as we have now become aware, were widely known and frequently the subject of comment in England and on the European continent. For this reason it should not surprise us that a reference to Addison's work rather than that of Waller appeared in Cohnheim's paper.[1] In the English literature, on the contrary, the name of Addison does not seem to have been mentioned in the context of Cohnheim's discovery until 1872, whereas Waller's findings were brought to light almost at once, in 1868.[2] In Austria the similarity between the work of Waller and Cohnheim was pointed out in 1868 by an investigator who predicted that oblivion would swallow the one as the other.[3] And what of Addison and Waller themselves? Did either one call attention to his work and make a claim to priority with respect to Cohnheim's findings? The answer, as far as the written record is concerned, seems to be in the negative.[4]

The plan of the present work does not allow room for an extended survey of the reception given Cohnheim's paper of 1867. We shall confine ourselves to matters that are relevant to the work of Addison. Firstly, we shall examine some of the attempts made to give significance to the movement of leucocytes from inflamed vessels and briefly note the re-surfacing of an idea once championed by Addison. Secondly, we shall examine Cohnheim's conception of the nature of the inflammatory process and attempt to bring it into relation with Addison's later views. In the course of doing so attention will be given to the contents of Addison's last work, *The Co-Existence of Two Species of Inflammation*, which was published in 1868.[5]

We recall at this point Addison's claim, put forward in the eighteen forties, that nutrition and growth are mediated by the passage of colourless 'embryonal' cells from the blood to

the tissues. Waller, on the other hand, without ascribing any physiological or pathological significance to the cells in question, had merely shown that white cells pass through apparently intact vascular walls and supposed that in this way the cells of pus and mucus originated. What was Cohnheim's opinion on the role of the white cells? In 1867 he stated that it was not his aim to account for all that occurred during the inflammatory process, much less to formulate a new theory of inflammation. Least of all, he wrote, was he in a 'position to give an explanation of why it is that the extravasated blood corpuscles always betake themselves to the site of the irritant'.[6] But a few of the investigators who followed him attempted to shed some light on this matter. For example, Kremiansky, a Russian working in von Recklinghausen's laboratory, inferred from the presence of vermilion particles in spindle-shaped cells found in corneal and other scars that leucocytes were transformed after emigration into connective tissue cells.[7] Other investigators attempted to explain the regeneration of damaged muscle or nerve and the re-epithelialization of skin and mucus membrane surfaces along the same lines. A good critical review of the subject came from the hand of Arnold Heller in 1869. He pointed out the inherent error in inferring from the presence of artificially induced pigmentation in a tissue cell that the cell in question was a transformed, emigrated leucocyte. The colourless cells of the blood were not the only cells capable of ingesting pigment. There was also the possibility that pigment might be transferred from one cell to another. Heller himself was unable to confirm the regenerative significance of extravasated leucocytes.[8] And Virchow, commenting on experiments of this kind in 1871, remarked that recent investigators had unwittingly revived the old notion of Zimmermann that all new formation of tissue was traceable back to extravasated white blood corpuscles. Some investigators, remarks Virchow, have 'referred the growth of epithelial tissue back to wandering cells, others have supposed connective tissue, muscle and nerve to be derived therefrom'.[9] Zimmermann's belief,

like that of Addison, represented an updated version of the theory of nutrition upheld in the eighteen twenties by Doellinger, Dutrochet and others, as we have already seen.[10] In a way, then, the wheel had come full circle. The 'intercalatory' or 'corpuscular' theory of growth processes had yielded to the blastema theory and was now, after that theory itself had yielded to Virchow's *omnis cellula a cellula*, briefly making a reappearance in hardly altered form.

Before examining Cohnheim's idea, or rather succession of ideas, of the significance of the inflammatory process we turn briefly to Addison's last work. *The Co-Existence of Two Species of Inflammation* was in all probability written before he could have learned of Cohnheim's experimental confirmation of his old hypothesis. As we have seen, it is unlikely that Addison read German, and the first notices in English of Cohnheim's demonstration did not appear until well along in 1868. In any case, there is no reflection of Cohnheim's disclosure to be found in the book. Nor does it ring any significant new variations on Addison's stock of themes. As before, he does not speak of the movement of white blood cells through vascular walls but of the 'retrograde metamorphosis' of these walls and the associated 'deciduous' growth of pus cells. Nowhere in it does he clearly and unequivocally state that pus or mucus corpuscles begin their careers as colourless blood cells. He does say that pus cells in unhealthy inflammation are 'charged with morbid matter from the blood', whereas the cells of healthy inflammation are 'prepared to take part in the metamorphoses required for the restoration of the solid tissues'.[11] Clearly, Addison is still committed to the intrinsic (Hunterian) combination of repair of injury with inflammation. The microscope, according to Addison, does not allow us to distinguish healthy from unhealthy inflammatory processes. On the contrary it shows that 'both comprise the same things, viz.—vascular cell-growths and detached cells swimming in a fluid,—*granulations* and *pus*'.[12] The surface of a healthy granulating wound discharges healthy pus cells 'because Nature always works with an excess of material'.[13] The

surface of an unhealthy ulcer, on the other hand, gives off pus cells that 'have been appropriated to the discharge of impurities from the blood'. And it is Addison's opinion that 'what can be seen in external parts affected with inflammation, is applicable to inflammation in internal parts; and we have called the action issuing in healthy cells, common inflammation, and that which issues in morbid cells, from blood impurity, specific inflammation'.[14] These are Addison's two species of inflammation. The character of the impurities responsible for 'specific' inflammation varies from case to case. At one time the disorder of the blood results from the presence therein of a specific poison, e.g. that causative of smallpox, at another improper diet is responsible. 'Suppressed secretions' and 'strong emotions' are also capable of producing the toxic effect.[15]

It is important to grasp the fact that for Addison inflammation, whether common or specific, is a fundamentally beneficial, physiological, process rather than a merely accidental concatenation of events resulting from a particular cause or set of causes. Some physicians, he writes, do indeed 'regard it as an unmitigated evil to be combated and subdued whenever it appears, others, perceiving its mixed characteristics of good and evil, approach nearer to the appreciation of its physiological purport'.[16] In local injury and in many instances of febrile disease 'the physiological purport of inflammation is conceded, and in such examples its well known pathological inconveniences are regarded with complacency'.[17] But Addison holds that the entire process of inflammation is governed by a general law and purpose aimed at preserving the life of the organism: 'Nature has the action of inflammation in reserve, not for the purpose of vexing mankind and shortening life, but for the purpose of repair and healing,—the cure of wounds and fractures, the discharge of dead parts and foreign bodies, and for elimination of unwholesome poisonous matters from the blood.'[18]

We may now compare Addison's ideas on the physiopathological significance of inflammation with those of

Cohnheim. In doing so it will be necessary to distinguish Cohnheim's earlier from his later ideas on this subject. We saw that in 1867, while still working under Virchow, Cohnheim disavowed any intent of setting up a new theory of inflammation. And with respect to the crucial point of his demonstration, Cohnheim attempted to soften its impact on Virchow's firmly seated belief that the cells in question arose from the division of locally present connective tissue cells (or of epithelial cells on mucus membrane surfaces). The new cells did indeed arise as the result of proliferation, said Cohnheim. Proliferation took place, however, not at the site of local inflammation but in the neighbouring lymph nodes and in the spleen. 'We see,' he wrote, 'that it is only necessary to modify the current view so as to transfer the site of new cell formation from the connective tissues into the lymph glands and spleen. . . .'[19] Virchow himself, said Cohnheim, had for a long time insisted on the necessary relationship between the increased number of leucocytes in the blood and the associated enlargement of lymph nodes and spleen that so frequently accompanied local inflammation.[20] But what did all these changes mean? Were they physiopathological reactive adjustments aimed at the preservation of the whole organism, even at the expense of damage to local parts, or were they pathological derangements pure and simple? Cohnheim gave no explicit answer to the question in 1867, although he was to do so at a later date.[21] His belief that the outward passage of white cells involved active, 'amoeboid' movements on their part as they traversed intact venular and capillary walls obviously carried with it an implied need to explain why the cells made their exit at sites of inflammatory activity, but he had none to offer. This belief, was soon to undergo a change, due in large part to the work of a young pathologist at Königsberg, Simon Samuel.

Samuel's first publication on the subject of inflammation appeared with Cohnheim's famous paper of 1867.[22] Introducing a new animal preparation to experimental pathologists, Simon applied croton oil to the ears of rabbits and observed the affected vessels in the resulting zones of in-

flammation. He did not, of course, see the outward passage of white cells. His attention was directed at that well-known phenomenon, the separation of white cells from the bloodstream and their accumulation on the walls of small vessels. This phenomenon, Samuel noted, occurred in the absence of any visible 'nutritional anomaly, exudation, swelling or cloudiness, in short without an alteration other than that described in the veins'.[23] The 'alteration' referred to here was simply the accumulation of white cells, but Samuel was shortly to give the term a different meaning. Even here, however, the implication that a local affection of the vascular wall might be central to the inflammatory process is present. In 1870, after he had learned of Cohnheim's findings, Samuel returned to the subject of inflammation. He attempted now to show that the outward movement of white blood cells through the walls of small veins depended not on amoeboid movements, as Cohnheim believed, but on an increase in lateral pressure combined with a loosening in the structure of the walls themselves. Samuel referred to the hypothetical change in the vascular wall as an *Alteration*, a term that was subsequently adopted by Cohnheim. It was Samuel's opinion that the partial dissolution of the wall allowing the leucocytes to move outward might be due to some chemical change in the tissue fluids adjacent to blood-vessels at sites of inflammation.[24]

By 1873 Cohnheim had decided that his original account of the factors responsible for the margination and outward movement of white cells was incorrect.[25] Adopting Samuel's term and idea he admitted that in 1867 he had overlooked a factor crucial for the entire inflammatory process, namely, a change in the structure of the walls of small vessels. Rejecting his earlier assumption that the amoeboid white cells actively 'wandered' out of the bloodstream into the tissues, he now no longer speaks of their emigration through intact vascular walls. For in his opinion the walls are not intact and the outward movement of cells is passive rather than active. Although Cohnheim did not stress the point, he was no longer under an obligation to give a

physiological meaning to the outward movement of white cells. Inflammation was a purely pathological process set in motion by physical and chemical agencies capable of producing the required 'molecular lesion' (Cohnheim thought it unlikely that the lesion was a microscopically visible one) of the vascular wall. Aside from physical and chemical agencies were there any other factors operative? Cohnheim comments at this point that in the 'bacteria-happy' (*bacterienfroh*) year of 1873 there are investigators who have assigned to these micro-organisms an important role as agents of inflammation. But as for himself he regards the hypothesis as hardly probable.[26]

One final question remains. Did Cohnheim regard the entire process of inflammation as no more than the accidental result of a particular kind of damage to the walls of small blood-vessels? Was inflammation, for him, merely a 'disease' and in no way a restorative or protective process, an aspect of the self-regulating power of living organisms? The answer is somewhat complicated. Insofar as the outward movement of cells and fluid through altered vessel walls at sites of inflammation was concerned it appears that in 1873 Cohnheim regarded these events as no more regulatory or protective than would be a break in the pipelines of a mechanical hydraulic system. But, like any physician, Cohnheim was aware that the inflammatory process associated with fractures and injuries in general usually did regress, with or without intervention by the physician. Further, he could not entirely separate repair, regeneration and healing from inflammation proper, i.e. from the immediate results of the vascular lesion, since one set of events flowed imperceptibly into the other. In his lectures on general pathology, first published in 1877, Cohnheim rejected the view that muscle, nerve and epithelium were derived from white blood cells of the inflammatory exudate. He did suppose, however, that the extruded white cells gave rise to fibrous tissue—scars, fibrous adhesions between serous membrane surfaces in the pleura and peritoneum, bony callus in the case of fracture, and so on. He pointed

out that at times, notably in the case of bone fractures, the newly formed tissue was extremely useful to the organism. In other instances it was less so or not at all.[27]

For some reason Cohnheim chose to elaborate this point in the second edition (1882) of his lectures. He now finds that it 'would indeed not be a very difficult task, given the remarkable adaptation of our organization to ends to show that our body could react in no better and more advantageous way to the harmful agent concerned that arouses inflammation than with precisely the inflammatory circulatory disturbance; yet our science has been so flooded with considerations of this sort during the past decades that today they enjoy little esteem'. Cohnheim then repeats, as in the first edition, that it is clearly advantageous to the organism for wounds to become united or noxious objects encapsulated by fibrous tissue, although on the other hand the harm occasioned by fibrous adhesions in the pericardial or peritoneal cavity is equally plain.[28] The statement is puzzling, for no reason at all is apparent why Cohnheim now sees fit to call the inflammatory circulatory disturbance a 'reaction' on part of the body and a highly advantageous one at that. As before, the only 'advantage' that he ascribes to inflammation is fibrous union, seen at its best in the events leading up to the union of fractured bones; this can hardly be called advantageous when peritoneal or pericardial adhesions result, as Cohnheim himself has already stated. In what other sense is the circulatory disturbance of acute inflammation advantageous other than that in some circumstances certain of the emigrated cells may become transformed into advantageously situated connective tissues? Cohnheim nowhere tells us. And why does he now call inflammation a 'reaction' aroused in the organism by a harmful agent when before he had gone to such pains to explain the entire sequence of events in acute inflammation as the inevitable mechanical result of a molecular lesion in the walls of small vessels? The clear inconsistency of the statement in the second edition of the lectures with what had gone before suggests that Cohnheim was in the process of changing his

mind. But we can do no more than guess at his reasons. Any thoughts that he may have had on the subject were interrupted by his death, following a long illness, in 1884.

Bibliography and Notes

1. It is apparent that neither Virchow nor Cohnheim was at this time really conversant with Addison's work. The 'exact and true observation' referred to by Cohnheim in his footnote, did not in fact exist. It was, as has been pointed out, merely a hypothesis. In the 1st (1858) and 2nd (1859) editions of *Die Cellularpathologie* Virchow writes of the question 'seriously raised by Addison and Zimmermann, whether pus corpuscles are not merely extravasated colourless blood cells, or vice-versa whether the colourless blood cells found within the vessels are not pus corpuscles that have been admitted into them from the exterior'. He concludes that the two kinds of cells can be distinguished only on the basis of their origin. If the origin is unknown, 'you may conceive the greatest doubt as to whether you are to regard a body of the kind as a pus or a colourless blood corpuscle' (Chance's translation, p. 188). In fact, however, Addison proposed only the first of the two alternatives. In a later chapter of the 2nd edition Virchow states, with respect to the distinction between pyaemia and leucocytosis, that 'some have thought they saw pus when they had colourless blood corpuscles before them, whilst Addison and Zimmermann, on the contrary, imagined they had found colourless blood corpuscles when they were really looking on pus' (ibid., p. 527). In the 4th edition (1871) Zimmermann's name does not appear in the first of the above citations (Ch. VII in the 1st and 2nd editions, Ch. VIII in the 4th) and Virchow puts Addison together with James Paget in line with William Hewson's late eighteenth-century views on the 'plastic lymph'. Virchow writes: 'This doctrine of lymph exudation has been proposed in particular by W. Addison and Paget, and it has recently won some firm factual underpinning in connexion with the colourless corpuscles.' In the revised version of the doctrine, says Virchow, '"lymph corpuscles" pass out together with the "plastic lymph"' (4th edition, p. 188). Virchow goes on to mention the descriptions of amoeboid movements and uptake of particles by colourless cells given by Wharton Jones, Ernst Haeckel and von Recklinghausen, and then adds that 'Waller and Cohnheim finally observed under the microscope the emigration [*Auswanderung*] of colourless blood corpuscles from the vessels of living animals on to surfaces and into the surrounding tissues . . .' (ibid., p. 189). We see that Virchow has now become aware that it was Waller, rather than Addison, who had anticipated Cohnheim. The linking of Addison to Hewson and the idea of the plastic lymph suggests also that Virchow may

have become acquainted with Addison's later attempt to bring his views into line with the doctrine of 'plastic lymph' (cf. Ch. III.2). Virchow's final reference to Addison in the 4th edition occurs in the context of an interesting, if slightly short-sighted, historical excursus. He writes: 'The question of pus formation has in the course of time become rather complicated. While recent observers for many years regarded it as a foregone conclusion that pus corpuscles arose from the exudate by spontaneous generation a few investigators, such as William Addison and Gustave Zimmermann, first put forward the opinion that pus was essentially to be derived from extravasated colourless blood corpuscles (lymph corpuscles). Benno Reinhardt, on the other hand, showed that the cells presenting in the secretion of wounds during the first few hours did indeed correspond to those presenting in the blood at the same time, yet that later this was no longer the case. Nevertheless he too allowed these subsequent pus corpuscles an origin in the exudate. But after I found it necessary to explain what he regarded as the beginnings of young pus corpuscles as in fact later products arising within older corpuscles [i.e. ingested material] I had to insist that not all elements found in pus stem from the blood. Meanwhile the investigations of Waller and especially of Cohnheim have shown to what a great extent this is the case. In addition, the latter has found by direct observation of the frog mesentery, that the outward passage of colourless blood corpuscles does not take place by passive exudation but by active emigration, predominantly indeed through the walls of smaller veins, and although this fact has been sharply disputed by many opponents there can nevertheless not be the slightest doubt with regard to its accuracy, in accordance with what I myself have seen' (4th edition, pp. 530, 531). Virchow went on to warn against the notion that *all* cells in inflammatory exudates were emigrated white cells. Some arose due to local proliferation (ibid., p. 531).

2. An editorial in the *Lancet*, 18 April 1868, carried a favourable account of Cohnheim's work. On 2 May 1868 a reminder came from a Dr. Sharpey (probably William Sharpey, the anatomist and physiologist) that Cohnheim's findings had been 'promulgated some twenty years ago by Dr. Augustus Waller'.
3. Kolomon Balogh, 'In welchem Verhaeltnisse steht das Heraustretung der farblosen Blutzellen durch die unversehrten Gefaesswandungen zu der Entzuendung und Eiterung', *Arch. path. Anat. Physiol. klin. Med.*, 1868, **45**, 19–37. Balogh failed to find either margination or emigration of white cells in inflamed vessels. The observations of Waller and Cohnheim were optical illusions, he stated, and pus cells could quite clearly be seen to arise from connective tissue cells.
4. Waller died in 1870 and Addison in 1881. I have found no evidence of a response by either man to Cohnheim's paper of 1867.
5. William Addison, *The Co-Existence of Two Species of Inflammation, With Special Reference to the Forms of Pneumonia*, London, 1868.

6. Cohnheim, loc. cit., p. 76.
7. Jacob Kremiansky, 'Experimentelle Untersuchungen ueber die Entstehung und Umwandlung der histologischen Entzuendungsprodukte', *Wien. med. Woch.*, 1868, **18**, 5–7, 23, 24, 37–39, 53–55, 70–73, 83–87.
8. Arnold Heller, *Untersuchungen ueber die feineren Vorgaenge bei der Entzuendung, nach fremden und eigenen Experimenten*, Erlangen, 1869.
9. Virchow, *Die Cellularpathologie*, 4th ed. (1871), op. cit., p. 390.
10. Cf. Ch. II.1.
11. Addison, *The Co-existence of Two Species of Inflammation*, op. cit., p. 22.
12. Ibid., p. 9.
13. Ibid., p. 22.
14. Ibid., p. 23.
15. Ibid., pp. 7, 24.
16. Ibid., p. 25.
17. Ibid., p. 26. This recalls Stahl. Cf. Ch. III.2, note 26.
18. Ibid., p. 30.
19. Cohnheim, *Entzuendung und Eiterung*, op. cit., p. 74.
20. Ibid. But in fact Cohnheim's statement, 'without vessels, no inflammation' (*Ohne Gefaesse keine Entzuendung*) is incompatible with Virchow's essentially cellular theory of inflammation.
21. Virchow's interpretation of the significance of the inflammatory response may be pertinent here, since Cohnheim was no doubt well acquainted with it. In the *Handbuch der speciellen Pathologie und Therapie*, vol. 1, pp. 46–94 (Würzburg, 1854) Virchow gives his views in full. (Due to its special character *Die Cellularpathologie* is not as satisfactory a source.) They may be summarized as follows: Inflammation is a local disturbance of nutritive relationships between blood and tissues. Physical, chemical or organic agencies (termed *irritantia*) give rise to passive disturbances (*irritamentum*) of cells or groups of cells. The injured cells respond actively (or reactively) in an essentially physiological way and give rise to the series of events comprised under the heading of inflammation. But the therapeutic value of the inflammatory reaction is always problematic, says Virchow. The simple teleological interpretation asserts that inflammation represents a defensive battle of the organism against harmful agencies of internal or external origin. Although this interpretation overshoots the goal it must be admitted that some features of the inflammatory response can be regarded as attempts to restore physiological equilibrium. On the other hand the reaction may be of such magnitude as to carry in its train dangerous disturbances of function. What distinguishes the inflammatory response is its destructive tendency and 'characteristic of danger' (*Charakter der Gefahr*).
22. Simon Samuel, 'Versuche ueber die Blutcirculation in der acuten Entzuendung', *Arch. path. Anat. Physiol. klin. Med.*, 1867, **40**, 213–24.
23. Ibid., p. 216.
24. Ibid., 'Ueber Entzuendung und Brand', *Arch. path. Anat. Physiol. klin.*

Med., 1870, **51**, 41–99, 178–209. Samuel was by no means the first to reject this aspect of Cohnheim's explanation (cf. Heller, loc. cit.).

25. Julius Cohnheim. *Neue Untersuchungen ueber die Entzuendung*, Berlin, 1873. After having held the chair in pathological anatomy at Kiel from 1868 to 1872, Cohnheim was at this time professor at Breslau.
26. Ibid., p. 84. The bacteriological era had barely commenced. Cohnheim's reference in this connexion is Edwin Klebs' *Beitraege zur pathologischen Anatomie der Schusswunden*, Leipzig, 1872.
27. Julius Cohnheim, *Vorlesungen ueber allgemeinen Pathologie*, Berlin, 1877–80, 2 vols., vol. 1 (1877), pp. 191–306.
28. Ibid., 2nd ed., 1882, vol. 1, pp. 232–367.

IV Epilogue

IV.1 The White Cells as Phagocytes

Metchnikov's Biological Theory of Inflammation

The story of William Addison's involvement with the white blood cells, extending over a period of some forty years of the mid-nineteenth century during which modern medicine was taking form, would now seem to be concluded. And so in a sense it is. But we have, with the death of Addison in 1881, reached a time in the history of medical thought when the passage of white cells from the blood to the tissues, now almost universally accepted, is to receive a new rationale—or, rather, an old rationale is to be applied to new findings—and a new theory of inflammation thereby developed. Without a brief account of these events our story would be incomplete, the more so since many of the themes with which we have become familiar are about to be combined for a finale in what will seem an almost inevitable fashion. It will be convenient to defer a final assessment of Addison's life work until these events have been recounted.

According to the new interpretation offered in 1883 by Ilya Metchnikov and designated by him the 'biological' theory of inflammation, the essence of the inflammatory response, up and down the phylogenetic ladder, consists in the arrival on the scene of tissue damage of certain specialized cells that ingest, digest and dispose of foreign bodies or invading micro-organisms responsible for the damage. These specialized cells he called 'phagocytes' (Greek, *phagein*, to eat) and in man they included the familiar colourless corpuscles found in the blood and tissues. Metchnikov traced the phagocytic activities of cells as phylogenetically far apart as those in plasmodia, water-fleas, larval starfish

and man. Inflammation, he asserted, must be 'regarded as a phagocytic reaction on part of the organism against irritants . . . carried out by the mobile phagocytes sometimes alone, sometimes with the aid of the vascular phagocytes . . .'.[1] In its simplest form, in the water-flea *Daphnia* for example, the inflammatory reaction took place in the absence of a vascular system and consisted in the ingestion, digestion and disposal (if the defence was successful) of the irritant by wandering, amoeboid phagocytic cells that patrolled the tissues. In animals with vascular systems, such as the vertebrates and man, white blood corpuscles constituted the chief supply of protective phagocytes. They were brought by the bloodstream to sites of irritation (most often due to the activities of micro-organisms) where they passed through the walls of minute vessels and attacked and devoured the bacterial foe. After a long period of debate and disagreement, never fully resolved, Metchnikov's biological theory gained a place among the accepted doctrines of medical science that it has continued to hold until the present day.[2]

We have seen that Addison interpreted inflammation as a healing and protective response, mediated in some way by cell activities, on the part of the organism. As far as the first part of his thesis was concerned it was well within the medical tradition and was no doubt shared by a large number of his colleagues in England. In Germany, on the other hand, attempts to explain biological events in terms of ends and purposes—so-called teleological explanations—had fallen into disrepute among scientifically minded physicians. The essentially teleological interpretation of the inflammatory process as a 'defence reaction' had to a considerable extent come under this ban. Henle had in fact rejected the venerable interpretation of the disease process as a whole as a kind of warfare between 'good' and 'evil' forces.[3] But the old idea that harmful foreign matter, a *materia peccans* or *materies morbi*, was discharged in pus rested on a firm empirical basis. Everyone could observe for himself how a thorn, or other foreign body embedded in the flesh, excited suppuration which was followed by

extrusion of the thorn and rapid subsidence of the local disturbance. The idea inherent in this everyday observation had long since been generalized, and van Helmont in the early seventeenth century had introduced the notion of a 'metaphorical thorn', a hypothetical substance capable of arousing and supporting internal inflammatory disease.[4]

In our survey of Addison's papers on the therapeutic powers of cells we found Virchow in the eighteen forties putting aside as anachronistic and anthropomorphic a comparison (made by persons unknown) of the activities of pus corpuscles to those of police officers charged with the task of expelling or imprisoning foreign agents.[5] It is revealing, with respect to the way in which the human mind works, to find that the idea contained in the comparison was revived and presented in connexion with a rather speculative 'germ' theory of disease no sooner had Cohnheim's findings become known. Joseph G. Richardson, a pathologist in Philadelphia, wrote in 1869 that he had confirmed Cohnheim's equation of pus, mucus, salivary and white blood cells. He called attention also to Lionel Beale's hypothesis that certain refractile particles seen in salivary corpuscles might be the 'germs of bacteria'. Richardson then added: 'If the hypothesis thus guardedly endorsed by the celebrated English microscopist be correct, it seems not improbable that the white corpuscles, either in the capillaries or lymphatic glands, collect during their amoebaform movements, those germs of bacteria which my own experiments . . . indicate always exist in the blood to a greater or lesser amount.' In this way the beneficial effects of therapeutic measures leading to the discharge of such corpuscles could be explained, Richardson thought, for 'it appears not impossible, that when thus loaded, their elimination through the saliva, under the mercurial influence, and their evacuation by a discharge of pus from a seton or tartar emetic ulcer, really constitute that therapeutic value of these remedial measures in certain cases which has long rested unexplained'.[6]

We noted previously that the therapeutic value attached

to suppuration by medical tradition made it likely, once the essential constituent of pus had been recognized under the microscope as the pus cell or corpuscle, that someone would assign the supposed therapeutic effect to some activity of these cells. As for the 'germs of bacteria' mentioned by Richardson (following Beale), the notion had been abroad for centuries that minute living organisms, *contagia viva*, were the causative agents of contagious diseases. Although it did not become established on a sound empirical basis until around 1880 the hypothesis had been rather thoroughly worked up in 1840 by Henle, at a time when the only known causative agent falling into this category was a fungus responsible for a disease of caterpillars. As far as inflammation was concerned the hypothetical micro-organism constituted, for Henle, another variety of the old 'metaphorical thorn'.[7] If we add to this complex the demonstration by Cohnheim in 1867 that white blood cells passed out into the tissues and on to mucus membrane surfaces a remark along the lines of that actually made by Richardson in 1869 was perhaps to be expected.

Richardson implied that the germs in question were engulfed by white cells in the same manner that amoebae engulfed particulate matter in the surrounding fluid. But he had nothing to say about the fate of the engulfed particles other than that they were, so to speak, conducted over the border. Thirteen years later, after the bacteriological era was well under way, George Sternberg, an American bacteriologist, included the idea of digestion in the complex. 'It has occurred to me,' he wrote in 1883, 'that possibly the white corpuscles may have the office of picking up and digesting bacterial organisms when by any means they find their way into the blood.' Further, the 'propensity exhibited by the leucocytes for picking up inorganic granules is well known, and that they may be able not only to pick up but to assimilate, and so dispose of, the bacteria which come in their way does not seem to be very improbable in view of the fact that amoebae, which resemble them so closely, feed upon bacteria and similar organisms.'[8]

Alternative interpretations of the activities of white cells were not of course ruled out. We saw that Cohnheim was not at first inclined to place much credence in the belief that bacteria were important causes of inflammation and of disease generally. By 1877 his mind had changed.[9] But at no time did he suggest that white cells played a role in the defence of the body against bacteria. The presence of micro-organisms within white cells attracted the attention of an increasing number of investigators in the late eighteen seventies, when the introduction of aniline stains at about this time made their identification easier and more precise. But the presence of large numbers of bacteria within white cells could be and was interpreted in quite another sense than that adopted by Richardson. Robert Koch, for example, remarked in 1878 that the relation of certain micro-organisms to the white cells was 'puzzling'. 'They penetrate into them,' he wrote, 'and multiply in their interior.' In some instances, he found, 'there is hardly a single white corpuscle in the interior of which bacilli cannot be seen'.[10] Koch was at the time studying the micro-organisms thought by him to be responsible for wound infection, but he was far from drawing the conclusion that white cells were engaged in a defensive battle against these organisms. Metchnikov in fact found Koch to be extremely cool, not to say hostile, to the new theory.[11]

In view of the steps taken by medical investigators in the mid-nineteenth century apparently pointing toward a theory of inflammation that would pit white cells against invading micro-organisms it is ironical that the man who founded this theory should have been recruited by the forces of history from entirely outside the ranks of the medical profession.[12] Ilya Metchnikov was a professor of zoology at the University of Odessa whose interest lay in the digestive process as it took place in lower animals. His first paper on this topic, published in 1878, dealt with the behaviour of wandering amoeboid cells found in the tissues of the marine sponge. These cells (which had already been studied by Lieberkühn in 1857) ingested, dissolved and subsequently ejected the

residues of food particles that had entered the pores and channels of the sponge.[13] Metchnikov's interest in the activities of such cells—the *Fresszellen* of the German writers or 'phagocytes', as he himself was later to call them—eventually led him to turn, in mid-career, from the field of zoology to that of human pathology. He knew relatively little of what medical investigators and theorists had to offer on the subject of the white blood cells and their role in inflammatory processes. While his ignorance may have been in part responsible for the polemics that marked his later career, it is likely that a more important reason was the same intellectual one-sidedness that was his chief source of strength. Metchnikov was the scientific hedgehog *par excellence*, the man who knew one big thing and who attempted to derive everything else from it. And that 'one big thing', about which his scientific life revolved, was the fundamental importance and the far-reaching scope in the animal economy of the activities of mobile, phagocytic cells.[14]

The birth of Metchnikov's ideas on inflammation and the turning point of his scientific career took place in 1882. Following the assassination of Alexander II, Metchnikov, who was himself apolitical, resigned his post at Odessa (where student and faculty unrest was at the time extreme) and travelled to Sicily with his wife and children. At Messina he was able to pursue his studies on marine animals in peace. Metchnikov described the decisive events that then took place as follows. One day, while his family was at a circus enjoying the performance of some trained monkeys, he had turned to his microscope to proceed with his observations of wandering amoeboid cells, in this case in the transparent tissues of the larval starfish. Suddenly a thought came to him. What if these same cells served to defend the starfish against harmful intruders? If so, a splinter introduced into the body of the larval starfish, a creature devoid of blood-vessels or a nervous system, ought to be quickly surrounded by mobile mesenchymal cells, somewhat as a splinter in a man's finger was surrounded by

pus corpuscles. 'From the small garden of our house,' writes Metchnikov, 'a small garden in which we had set up a "Christmas tree" on a little tangerine tree a few days before, I took several thorns from a rose in order to introduce them beneath the skin of these superb larval starfish, as transparent as water.' He did not sleep that night, in expectation of the outcome of his experiment. On the following day at an early hour in the morning, he 'ascertained with delight that it had clearly succeeded'. This experiment, said Metchnikov, 'served as the foundation of the theory of phagocytosis, to the development of which I devoted the following twenty-five years of my life'.[15]

According to another account of these events given by Metchnikov, he had never pursued any medical studies until shortly before leaving for Messina. At that time he became acquainted with Cohnheim's *Lectures on General Pathology*. He was struck, he said, by Cohnheim's description of the passage of white corpuscles through vessel walls. But he found Cohnheim's theory of inflammation to have an 'extremely vague and nebulous character'. Reflecting that the presence of white corpuscles in great abundance at sites of injury, left unexplained by Cohnheim, ought to have some important purpose (or function, to use a more neutral term) he guessed what it might be and devised the experiment with the larval starfish to test his assumption.[16] Metchnikov tells us that in 1882 he was aware that pathologists regarded inflammation as the consequence of bacterial activity in most, if not all, cases.[17] This led him to suppose that the 'diapedesis and accumulation of white corpuscles in inflammatory diseases must be regarded as modes of defence of the organism against micro-organisms, the leucocytes in this struggle devouring and destroying the parasites'.[18] He then read Ziegler's book on pathological anatomy and found 'a great number of observations fitted to facilitate the acceptation of the new hypothesis on inflammation and healing'.[19]

By a stroke of good fortune Virchow came to Messina in the spring of 1883. The two scientists met and Metch-

nikov showed Virchow preparations of starfish larvae, illustrating the phenomenon of inflammation in organisms lacking nervous and vascular systems. When Metchnikov explained that his theory of inflammation rested on the hypothesis that the white corpuscles 'gave chase to the micro-organisms and destroyed them', Virchow replied that the general opinion among pathologists was just the opposite —the micro-organisms within leucocytes were thought to be making use of these cells for transport and dissemination throughout the body. Virchow nevertheless encouraged Metchnikov to continue with his studies.[20] Metchnikov's first paper directed at a medical audience appeared in 1884 in a journal edited by Virchow, and in 1885 Virchow himself gave a favourable assessment of the new theory of inflammation.[21]

Metchnikov returned to Odessa in 1883. In the same year he gave for the first time a public account of his theory (in the course of a lecture on the natural healing powers of animal organisms), making the claim that phagocytes were the chief means of defence possessed by the organism against the agents of infectious disease.[22] At about the same time he contributed an article on the subject, with a wealth of illustrative material, to a European journal of zoology.[23] Although this article dealt chiefly with intracellular digestion in invertebrates, Metchnikov generalized his findings to include man. 'It seems therefore,' he writes, 'that indeed in the entire animal kingdom the wandering mesodermal elements use their activity of taking up and digesting nutriment for the protection of the organism against bacteria.'[24] The phagocytic cells had the function of taking up and consuming both those 'parts of the body that have become useless and foreign bodies that have forced their way in from outside, or, if this is not possible, at least of surrounding and holding them fast'.[25] In Metchnikov's opinion precisely the same kind of activity was central in the inflammatory process as it occurred in vertebrates. This fact had heretofore been concealed by the prominence of events—which now appeared quite subsidiary—involving the nervous and

vascular systems. Cohnheim's statement 'no vessels, no inflammation', said Metchnikov, could no longer be upheld. In the light of comparative pathological evidence the non-vascular form of inflammation was seen to be geneologically much older than the vascular form.[26]

In 1884 the new theory made its appearance in journals aimed at medical investigators. The first article, already referred to above, dealt with the phagocytic defence of *Daphnia* against an invasion of minute fungi.[27] The second, which contained a long exposition of Metchnikov's views, concluded with the statement that, contrary to the opinion of Cohnheim, inflammation was not a passive response of microvascular injury but an active response of cells to irritants, an 'activity of living cells in the sense of cellular pathology'.[28] The essence of inflammation had, once again, been found in a cellular response to injury.

Bibliography and Notes

1. Ilya Metchnikov, *Lectures on the Comparative Pathology of Inflammation*, London, 1893, trans. from the French ed. (1891) by F. A. and E. H. Starling. Reprinted with an introduction by Arthur M. Silverstein, New York, 1968, p. 189.
2. The 'finale' of the present monograph is by no means the finale of the history of inflammation or of the activities of white cells. The idea that the phagocytic response is a purely protective one has come under increasing fire during the past decade. In the so-called auto-immune diseases the circulating leucocytes seem to act, rather, as agents of tissue damage. Some doubt has also been cast on their importance in the initial stage of bacterial invasion. (On this subject see *The Inflammatory Process*, ed. by Benjamin W. Zweifach, Lester Grant and Robert T. McCluskey, New York, 1965.) See also note 28.
3. Max Neuburger, *Die Lehre von der Heilkraft der Natur im Wandel der Zeiten*, Stuttgart, 1926, pp. 182–90, quotes from Henle's *Pathologische Untersuchungen* (1840) and his *Handbuch der rationellen Pathologie* (1846) at length. The following is from *Handbuch*, as quoted in Neuburger: 'The medical myth also, like all religious ones, starts from a personal dualism in order to make the conflict of beneficial and harmful events plainly comprehensible. The devil of medicine is disease or, in scientific language, the stimulus of disease, the *materia peccans*, the harmful

matter that has intruded, the disease-organism . . . the angel of medicine is self-regulation, or the healing power of nature.'

The metaphorical idea of 'warfare against disease' waged by the forces of the body is not prominent in the Hippocratic-Galenic tradition, if indeed it occurs at all. The first use of it that I have been able to find is by Pierre Brissot early in the sixteenth century. With reference to the familiar Galenic expulsive faculty, Brissot states that when 'foreign substances' are in the course of being expelled from the body the faculty 'having set about more actively to drive out that which is attacking . . . at once forces out some blood and spirit into the afflicted part from parts situated above . . . the neighbouring parts uniting and sending, as it were, auxiliary troops to beat down the common enemy' (*vehementius aggressa quod infestat expellere . . . vicinis partibus conferentibus, ac veluti copias auxiliares ad deturbandum hostem communem*). The passage is from Brissot's *Apologia disceptatio*, Paris, 1622, pp. 65, 66 (first published, Paris, 1525). Even more explicit is Thomas Campanella's claim that, contrary to received opinion, 'fever is not a disease, but a battle against disease' (*Nobis autem neque definitio, febris, neque divisio, Medicis positae, probari queunt . . . febrem non esse morbum, sed bellum contra morbum, potestativa vi spiritus initum*), made early in the seventeenth century (*Medicinalium juxta propria principia*, Lyons, 1635, p. 598; cited by Neuburger, op. cit., p. 38). Campanella, following the older authorities, including Galen, links inflammation and fever together. He uses the above metaphor in speaking of one of the ways in which inflammation comes about, viz., 'by spirit contriving war against noxious things' (*spiritu bellum parante adversus noxias res*), ibid., p. 93. Although the use of artificially induced fever to 'combat' disease (as we would say now, making use of the still popular military metaphor) was described as early as the first century by Rufus of Ephesus, he did not express himself in these terms. The metaphor could easily have originated from a combination of the Galenic idea of expulsive powers possessed by the parts of the body with the older and very widespread idea of disease as an enemy to be cast out, but it apparently did not do so until late in the history of western medicine.

4. Writers on the subject of inflammation frequently use the familiar mode of discharge of embedded thorns as a paradigm. Addison is no exception. In *Cell Therapeutics* (op. cit., p. 5) he writes that 'when a thorn enters the flesh, if it be not speedily removed, abscess and ulceration will take place in the parts around, and thus the offending body is often cast out'. Again, in *The Co-Existence of Two Species of Inflammation*, he remarks that when 'thorns or other foreign objects have pierced the tissues and remain in them', they are subsequently discharged to the accompaniment of the regular series of phenomena constituting inflammation and suppuration (op. cit., p. 6). A very neat formulation of the whole complex of ideas was given by C. J. B. Williams in 1843: 'There is in organized

beings a certain conservative power which opposes the operation of noxious agents, and labours to expel them when they are introduced. The existence of this power has long been recognized, and in former days it was impersonated. It was the *archeus* of van Helmont; the *anima* of Stahl; the *vis medicatrix naturae* of Cullen. But without supposing it to be aught distinct from the ordinary attributes of living matter, we see its frequent operation in the common performance of excretion; in the careful manner in which noxious products of the body, and offending substances in food, are ejected from the system; in the flow of tears to wash a grain of dust from the eye; in the act of sneezing and coughing to discharge irritating matters from the air passages; and in the slower, more complicated, but not less obvious example of inflammation, effusion of lymph, and suppuration, by which a thorn or other extraneous object is removed from the flesh' (*Principles of Medicine*, op. cit., p. 7).

Van Helmont's 'metaphorical thorn', a hypothetical chemical substance responsible for pleurisy (*metaphorica . . . spina pleuritidis*) is discussed in his *Ortus Medicinae* (Amsterdam, 1652, p. 319). Thereafter the metaphor was taken up by medical writers, especially those in the iatrochemical tradition. But the 'thorn' can be traced back to a much earlier date. Galen, in a discussion of causes of disease of such nature that 'when they are present, the diseases too are present; when they are withdrawn, the diseases too depart' (so-called containing causes, *aitia synektika*), gives as an example a *skolops*. In Kühn's translation the Greek term is rendered as *spina*. *Spina* has the secondary meaning of 'thorn', although Galen may have meant to use the term in the more general sense of a sharp-pointed object. Van Helmont may have derived his *spina metaphorica* from this passage, directly or indirectly. Cf. Galen, *Opera Omnia*, ed. C. G. Kühn, Leipzig, 1821–33, reproduced Hildesheim, 1965, vol. 14, p. 692.

5. Cf. Ch. III.2, note 17.
6. Joseph G. Richardson, 'On the identity of the white corpuscles of the blood with the salivary, pus and mucus corpuscles', *Penn. Hosp. Rep.*, 1869, **2**, 249–54. Richardson stained the nuclei of salivary corpuscles with aniline red, a dye which had just been introduced. He described the corpuscles in question as cells containing one to four oval nuclei surrounded by cytoplasm filled with 'molecules'. He found similar cells, some of which exhibited amoeboid movements, in the urine of patients with cystitis. Lowering of the specific gravity of the urine inhibited their movements, and the cells then assumed a spherical form. The 'seton' referred to by Richardson was a strip of linen or some such material passed through the skin in order to produce and keep up a discharge of pus. Caustic substances were applied for similar purposes. In the treatment of ophthalmia, cephalalgia, epilepsy and various thoracic and abdominal diseases setons were still in use during the mid-nineteenth century, although less so than formerly. Cf. Robley Dunglison, *Medical*

Lexicon (Philadelphia, 1860, p. 837). In another paper, 'Experiments showing the occurrence of vegetable organisms in human blood' (*Am. J. med. Sci.*, N.S., 1868, **56**, 291–94), Richardson recalls Davaine's assertion that there is a 'close connexion between the appearance of bacteria in the blood and the occurrence of carbuncular disease'. Richardson suggests also that such agents may be responsible for the 'zymotic' diseases, diphtheria, scarlet fever and smallpox. He seems to be the first of the investigators to whom the idea later fully exploited by Metchnikov occurred. Still another was brought to light recently by Robert Herrlinger: John Müllendorf, who in 1879 spoke of the consumption (*Verzehrung*) of spirilla found within the leucocytes of patients with recurrent fever ('Die historische Entwicklung des Begriffes Phagocytose', *Ergebn. Anat. EntwGesch.*, 1956, **35**, 334–57).

7. Jacob Henle, *Von den Miasmen und Contagien*, 1840, reprinted in *Klassiker der Medizin*, Bd. 3, Leipzig, 1910. Henle says that a thorn discharged by suppuration will arouse suppuration anew if introduced into the tissues of another person. Suppose, he suggests, that such a thorn could multiply while in the body. Each one of its parts would be capable of arousing inflammation and suppuration (op. cit., p. 26). Henle suggests also that the organisms responsible for contagious diseases may be digested and destroyed in the stomach (ibid., p. 25), thereby perhaps linking digestive and defensive processes for the first time.
8. Cited by Gert H. Brieger in his introduction to the reprint of F. G. Binnie's translation of Metchnikov's *Immunity in Infective Diseases*, New York, 1968, p. xx. (The French original was published in 1901, the translation in 1905.) Brieger mentions Sternberg's claim that he expressed his idea verbally at a meeting of the American Association for the Advancement of Science in August 1881. In 1903, according to Brieger, Sternberg wrote that he had clearly stated the new theory of inflammation 'several years (1881) before Metchnikoff's first paper (1884)'. Although Metchnikov's first paper on the subject was in fact published in 1883 (see note 23) there is no reason to doubt that Sternberg arrived at his idea independently of Metchnikov.
9. Cohnheim accords about ten pages to bacteria as agents of inflammatory disease in the first edition of his *Lectures* (op. cit.). He reminds his readers that the 'parasitic theory' of the origin of diseases is still largely hypothetical, even though the anthrax bacillus and the trichina worm have been revealed as the causes of anthrax and trichinosis. On the whole Cohnheim is favourably disposed toward the germ theory of disease. He remarks that Henle's ideas on the nature of the *contagium vivum* have now achieved general acceptance, after a long period during which they were rejected.
10. Robert Koch, *Investigations Into the Etiology of Traumatic Infectious Diseases*, trans. by W. Watson Cheyne, London, 1880, p. 37; German original, *Untersuchungen ueber Wundinfektionskrankheiten*, Leipzig, 1878.

Here may be found a partial statement of the requirements (Koch's postulates) for a 'thoroughly satisfactory proof' of the bacterial origin of any given disease. The postulates are also contained *in nuce* in Henle's *Von den Miasmen* (op. cit.), and Koch studied under Henle.

11. According to Metchnikov he was given a very brusque reception by Koch in 1887 at the International Congress of Hygiene. Koch found Metchnikov's evidence inconclusive. He remarked that he himself was a hygienist rather than a histologist and that from his point of view it made no difference whether bacteria were found inside or outside of cells (*Elie Metchnikov: Souvenirs, Receuil d'articles autobiographiques*, trans. from the Russian by L. Piatigorski, with notes by A. Gaissinovitch, Moscow, 1959, p. 143).
12. The overlapping of interests between medical investigators and zoologists in the mid-nineteenth century was somewhat greater than it is today. The same remark applies to scientific journals.
13. Metchnikov's 'Spongiologische Studien' appeared in 1878 and 1879 in the *Zeitschrift für wissenschaftlichen Zoologie* (see reprint of his *Lectures*, op. cit., for a bibliography). Among others who had worked on sponges was the physician Lieberkühn, with whose paper of 1854 on the amoeboid movements of white cells we have already become acquainted (Ch. III.4). Lieberkühn showed that minute infusoria passing through the pores and canals of the sponge into its interior were engulfed by contractile cells and subsequently broken down ('Beiträge zur Anatomie der Spongien', *Arch. Anat., Physiol. wiss. Med.*, 1857, 376–403). Metchnikov was aware of this work (*Lectures*, op. cit., p. 47).
14. Alexander Besredka pointed out that every aspect of Metchnikov's work, even including his theory of ageing and his so-called optimistic philosophy of life, was a facet of a single *idée directrice*, that of the phagocytic digestive process (*Histoire d'une Idée. L'Œuvre de E. Metchnikoff*, Paris, 1921).
15. *Souvenirs*, op. cit., pp. 94–97.
16. *Immunity in Infective Diseases*, op. cit., p. 518.
17. Ibid., p. 519. Although micro-organisms were by that time much more important for pathologists than they had been in 1873, when Cohnheim dismissed their importance as hypothetical, Metchnikov's statement is somewhat exaggerated.
18. Ibid.
19. Ibid. Metchnikov refers here to Ernst Ziegler's *Lehrbuch der allgemeinen und speciellen pathologischen Anatomie und Pathogenese*. In the 2nd ed. (1882) Ziegler discusses the activities of wandering cells in the tissues, the diapedesis of white blood cells and the damage to vascular walls possibly caused by bacteria. He states that 'inflammation, aroused by bacteria, in the course of which a great number of living cells accumulate in the tissues, is very frequently able to suppress the invasion of bacteria'. Fixed cells in the affected tissues also contribute toward checking their growth. How this is done is not explained, but in favourable instances,

according to Ziegler, 'the bacteria are killed and the affection ends with healing' (op. cit., p. 323). In the 4th ed. (1885) Ziegler adds that the well-known 'fressenden Zellen' have been given the name phagocytes by Metchnikov, who has also confirmed an observation long since familiar to pathologists, namely, that in invertebrates, too, these cells play the role of scavengers under both physiological (as in the absorption of the frog's tail during metamorphosis) and pathological (as in the absorption of dead cells) conditions (op. cit., vol. 1, pp. 154, 155). In the 6th ed. (1889) Ziegler added nothing to his account of Metchnikov's work. As in previous editions he accepts the Cohnheim–Samuel theory. In 1892 he attacked Metchnikov's theory openly instead of passing over it in silence as heretofore. Metchnikov is, says Ziegler, 'so completely under the spell of his doctrine of phagocytosis that he is unable to make his own the standpoint that the physician and pathologist must accept in regard to the doctrine of inflammation'. (Presumably he meant the doctrine that inflammation was a disease requiring treatment.) Metchnikov 'arbitrarily posits as the hallmark of inflammation a pathological phenomenon that interests him' ('Historisches und Kritisches ueber die Lehre der Entzuendung', *Beitr. path. Anat. allg. Path.*, 1893, **12**, 152–205; this passage is quoted in part by Metchnikov in the *Lectures*, op. cit., p. 205). It was undeniable, said Ziegler, that the elimination and destruction of parasites was at times favoured by the accumulation of cells and exudate, but it was incorrect to overlook the dangers involved by the inflammatory process itself. Inflammation 'can in certain cases of infection be a useful and appropriate process, but it is not so in all cases, and it can just as well bring about more disadvantage than advantage' (loc. cit., pp. 204, 205). Ziegler regarded phagocytosis as an inessential feature of the inflammatory process, and he insisted furthermore that in 1874, eight years before Metchnikov, he himself had written on the subject of intracellular digestion. Metchnikov retorted that, in any case, the observation to which Ziegler referred had been made in 1871 by Bizzozero (*Lectures*, op. cit., pp. 210–11). As time passed Metchnikov became better informed with respect to developments in medical theory prior to the start of his own interest in the subject. At the time of writing the *Lectures* he apparently did not know of Hans Buchner's attempt to explain inflammation as a facet of immunity against infectious disease (*Die Naegeli'sche Theorie der Infektionskrankheiten*, Leipzig, 1877). Ten years later Metchnikov noted that Buchner regarded inflammation as a 'salutary reaction, which acts not directly on the exciting morbific cause, but through the mediation of the specific cells of the organs' (*Immunity in Infective Diseases*, op. cit., p. 513). For the phrase 'salutary reaction' see Ch. III.2, note 26.

20. *Immunity in Infective Diseases*, op. cit., pp. 519, 20.
21. Rudolf Virchow, 'Der Kampf der Zellen und der Bakterien', *Arch. path. Anat. Physiol. klin. Med.*, 1885, **101**, 1–13.

22. Metchnikov gives this account in Kolle and Wassermann's *Handbuch der pathogenen Mikroorganismen*, Bd. IV, T. 1, Jena, 1904, p. 361. The lecture is said to have reached print in a Russian journal, but I have been unable to locate it.
23. Ilya Metchnikov, *Untersuchungen ueber die intracellulaere Verdauung bei wirbelloser Thieren*, *Arbeiten aus dem zoologischen Institute der Wien*, T. V, Hft. II, Vienna, 1883, pp. 141–68.
24. Ibid., p. 20.
25. Ibid., p. 16. Cf. the view rejected by Virchow in 1847, Ch. III.2, note 17.
26. Ibid., p. 17.
27. Ibid., 'Ueber eine Sprosspilzkrankheit der Daphnien. Beitrag zur Lehre ueber den Kampf der Phagocyten gegen Krankheitserreger', *Arch. path. Anat. Physiol. klin. Med.*, May 1884, **96**, 177–95.
28. Ilya Metchnikov, 'Ueber die pathologische Bedeutung der intracellulaeren Verdauung', *Fortschritte der Medizin*, 1884, **2**, 558–69. (This issue carries on p. 557 an obituary for Cohnheim, who died on 14 August 1884.) The superfluous phrase 'im cellularpathologischen Sinne' is of course a polite gesture in the direction of Virchow. Both men, although in quite different ways, had reduced the inflammatory reaction to a cell response.

    A careful reading of this article shows that Metchnikov's idea of the inflammatory reaction as fundamentally protective was, from the beginning, not as simplistic as some of his opponents held. For example, with respect to a therapeutic manoeuvre suggested in 1869 by Carl Binz, viz., the inhibition of leucocytic migration by the use of drugs, Metchnikov stated that the procedure should be 'limited to cases where the phagocytes were devouring elements important for the integrity of the whole, as, for example, in atrophic diseases of the central nervous system'. In other cases, where the phagocytes were engaged in a fight against the agents of disease, 'their activity must rather be further heightened' (loc. cit., p. 569). Still later he came to the conclusion that unrestrainedly aggressive phagocytic cells were responsible for the pathological ageing of tissues (*The Nature of Man, Studies in Optimistic Philosophy*, London, 1903). Metchnikov denied that his theory was teleological. It was based, he said, on the 'law of evolution according to which the properties that are useful to the organisms survive while those which are harmful are eliminated by natural selection'. It was precisely because the phagocytic defence reaction was 'not a designed adaptation to a particular end, that cases naturally occur where the phagocytes do not fulfil their functions, a neglect followed by the most serious danger to or death of the organism' (*Lectures*, op. cit., pp. 193, 194).

IV.2 A Critical Assessment of William Addison

Our survey of Addison's published work having been completed and rounded off with some comments on a pertinent development in medical theory that took place shortly after his death, a final assessment of some kind is perhaps in order.[1] But with what criterion or criteria are we to proceed? Should we adopt one of more or less Humean character and consign to the flames everything in his writings that is neither a newly demonstrated matter of fact nor a piece of reasoning based on fully established facts? Little would remain if we were to do so. The foregoing pages will, I believe, have convinced the reader that none of the discoveries supposedly made by Addison stands up under close examination. He cannot be regarded as a precursor of Cohnheim (*pace* Virchow) insofar as the discovery of the outward passage of white blood cells is concerned—any more than Doellinger, Dutrochet, Kaltenbrunner, Zimmermann and all the others (with the single exception of Waller) who have been accorded this position. He was not the first to recognize the white cell as a normal denizen of the bloodstream. Nor did he for the first time describe leucocytosis, local or general, although he did contribute some valuable observations along this line. He was not the first to discern the blood platelets—indeed if he may be said to have seen them at all, it is in a very weak sense of the word. To call him the world's first haematologist, as McCallum did in 1907, is—when we consider the work of Wharton Jones and Paget in England and of Nasse in Germany alone—mere hyperbole. But on the positive side of the ledger there are also some entries. Addison's series of papers on the coagulation of blood in the early eighteen forties contain an account of the formation of the *crusta inflammatoria*, or buffy coat, superior to most of those then to be found in the literature. He was one of the very few who recognized the degree to which white blood cells took part in the formation

of the familiar 'inflammatory crust'. And when we turn to Addison's experimental observations on the microcirculation in the web of the frog's foot we find that his account of the accumulation of white cells on the margins of minute vascular channels—we cannot say 'walls', properly speaking, since Addison denied their existence as such at this time—demands our respect. Although his observations along this line were matched or even in some respects surpassed by those of Paget and Wharton Jones they were certainly superior to the account given by Virchow's implacable rival-to-be, John Hughes Bennett. It is of course true that the entire subject had been rather thoroughly gone into a generation before by investigators in Germany and France, and none of the English workers can be accorded priority.

In a study such as the present one aiming at a restoration of the dimension of historical reality to a scientist of former times, an implicit assessment of his achievement is already present. I doubt that a reader who has followed me this far is troubled by any great uncertainty regarding the proper place to be given Addison in the scientific pantheon. It is obviously a modest one. (Some may feel that he deserves none at all. My own opinion is that although the claim on the basis of which he occupies his present place is suspect there are legitimate reasons for leaving him in possession of it.) Nevertheless I propose, before bringing this essay to a conclusion, to add to the store of information on which an assessment may be drawn by briefly reviewing Addison's work in the light of its methodology, originality, consistency and contemporaneity.

Methodology: To what extent was the way in which Addison proceeded in his investigations worthy of the honorific title of scientific method? And to what extent did he explicitly formulate his method? Assuming that he had something to say on the subject of scientific methodology, this must of course be distinguished from the method implicit in his work. As it turns out, Addison was a great admirer of Francis Bacon (whose reputation reached its peak

in the mid-nineteenth century) and regarded himself as a follower of the Baconian inductive method. Bacon's name may be found here and there in several of Addison's early papers. On one of these occasions Addison remarked that his own views on the subject of nutrition (and therefore of inflammation) were deduced from certain Baconian 'glaring instances'. The observed behaviour of colourless corpuscles in irritated small blood-vessels was, he wrote, a 'glaring instance of the process of nutrition'.[2] Now in Baconian parlance a glaring instance (*instantia elucescentia*) is an observed instance, an observation in short, of such a kind as to clearly reveal the form or essence of whatever general process or phenomenon is under investigation. On the basis of instances of this kind Bacon seems to regard it as legitimate to frame hypothesis (although he avoids the term). A glaring instance, according to Bacon, shows the 'nature' which is under inquiry in its exalted or highest grade of potency (*in exaltatione sua aut summo gradu potentiae suae*).[3] For Addison the accumulation of white corpuscles in irritated vessels and their subsequent appearance between the condensed 'fibres' that in his opinion constituted the transitional zone between the parenchyma and the vascular channel was a 'glaring instance' revealing in one stroke the true nature or Baconian form of the nutritive process. It did so by revealing that process in an exalted or heightened state, i.e. as the inflammatory process. Another of Addison's glaring instances is the coagulation of the buffy coat of the blood. The compact fibrous 'tissue' thus formed becomes, in his opinion, paradigmatic with respect to the formation of tissue throughout the body. And this tissue is not, in Addison's opinion, formed from a blastema by a process bearing some resemblance to inorganic crystallization, but rather 'from the fibrillation and incorporation of the colourless elements of the blood'.[4]

Addison's sensitivity to methodological issues was, as we have seen, enough for him to separate his facts from his chief hypothesis in 1844 so as to make clear to his readers the foundation on which his theory of nutrition and inflammation

rested.[5] In spite of this effort the hypothesis, ironically enough, became in the minds of those who looked fleetingly at his writings later on, the factual discovery for which they honoured him. In 1850 Addison remarked to those who might consider his conclusions too 'speculative and theoretical' that in his opinion no aspect of human knowledge could be given a scientific form without the aid of a theory. He was aware, he said, that medical audiences were apt to be hostile to theory, largely because of abuses practised in the past, but he reminded them that abuse did not forbid use.[6] How well acquainted Addison actually was with Bacon's methodological writings is open to question. It is likely that he derived a good part of his understanding from a book by the well-known astronomer Sir John Herschel, a warm admirer of Bacon and a defender, as well, of the hypothetical method.[7]

So much for Addison on scientific methodology. But what method did he in fact employ? The answer seems to be that he followed the Baconian procedure, as he understood it. He made his observations, selected from among them several 'glaring instances', made a hypothesis and built up a theory that tied in nutritive with inflammatory processes. His theory was, as we have seen, an up-dated version of the old corpuscular or intercalatory theory, with its roots in the late eighteenth century and its most recent flowering in the work of Doellinger, Dutrochet and others in the generation of investigators immediately before Addison's time. Unlike Barry, who also confessed to the intercalatory theory, Addison gave the white blood cells rather than the red the central role in this revived account of tissue growth and maintenance. The weakness in Addison's procedure was that it did not lead him to make new observations, or even to verify his hypothesis that the white cells seen in inflamed tissues were derived from the circulating blood. We can hardly expect him to have tagged the white cells, as von Recklinghausen was to do two decades later, but he might easily enough have made Waller's observation. Addison's belief that the capillaries were wall-less channels may have

been partly responsible for the fact that he did not. In any case it is plain enough that he was no experimenter.

Addison's published work of the early eighteen forties does not suffer overmuch when it is compared to that of many of his contemporaries, and we have seen that it was given a respectful enough hearing in England, Germany and Austria. To the modern mind it suffers inordinately when compared to Waller's two papers on white cell diapedesis. The precision with which Waller delimited his problem and proceeded to its solution is striking. Leaving aside Waller's failure to exploit his work, it exemplifies one facet of the scientific method recommended by Virchow in 1847, namely the ascertaining of detailed matters of fact (*Detail-Untersuchungen*) rather than the elaborating of hypotheses into theoretical systems. Virchow recognized the utility of hypotheses—to him they represented the 'thought that must precede every rational action'—but he argued that pathologists had been in the past too prone to derive 'laws', descriptive of regularly recurring phenomena, from hypotheses rather than hypotheses from laws. And in this way, he said, they moved from hypothesis to hypothesis without ever touching factual ground.[8] To a considerable degree Virchow's charge applies to Addison. In order to move from an hypothesis back to the factual background of observation from which it was derived, consequences of the hypothesis had to be formulated as questions open to experimental answers. Addison did not proceed in this way. Virchow's comment on the matter (made in 1849) reveals how clearly he himself saw the central importance of the properly posed question. 'The scientific question,' he wrote in 1849, 'is a logical hypothesis based on a known law . . . experiment, itself implicit in the question, gives the answer.'[9] Claude Bernard said much the same thing in France sixteen years later: 'It is impossible to devise an experiment without a preconceived idea; to devise an experiment, we have said, is to put a question; one never conceives a question without an idea which invites an answer.'[10]

Moving ahead to the eighteen fifties and eighteen sixties

we find that as the vanguard of medical scientists applied itself more and more intensively to the obtaining of precise answers to clearly formulated questions Addison became more and more speculative in his approach to the problems that interested him. We need only compare his *Co-Existence of Two Species of Inflammation*, published in 1868, with Cohnheim's essay of the year before to see how great the disparity had become. The comparison is perhaps unkind, since Addison was after all a practitioner rather than a medical scientist. It is also possible that his health had begun to fail at about this time. But the personal reasons, whatever they may have been, for Addison's decline from such scientific eminence as he may be said to have enjoyed during the eighteen forties is beyond the scope of this book.[11]

Is there anything more to be said of Addison's method? We should perhaps note that he employed the comparative or analogical procedure, admittedly on a smaller scale than Metchnikov, when he adapted to his ends the work of phytologists and zoologists. The notion of 'metamorphosis', which he applied to nutritive and inflammatory processes, came from the former. From the work of zoologists and others interested in infusoria he derived the idea that the blood corpuscles, both white and red, were independent, living, and, as we would say, metabolizing organisms. Addison was by no means alone among investigators of his time in adopting the comparative biological approach. It is a mistake to suppose that the comparative method, together with insight into the interest in the wider reaches of biological phenomena first reached medical science with Metchnikov.

Originality: If science is regarded as a kind of granary of well-attested facts (or statements, in modern terms) and the successful scientist as one who contributes to its store, then the historian of science is likely to regard it as his task to determine who added to this store, when, and under what circumstances. Flailing his way through the immense heap of past scientific writings he may see himself as one who—like the scientist himself—winnows grain from chaff. Ori-

ginality, from this point of view, consists in the discovery of new facts. If, on the other hand, we accept the idea that scientists are not isolated individuals engaged in discovering new facts or making new observations, but social beings whose endeavours are directed toward the solving of problems that have arisen within the context of an established body of knowledge (most of which they have acquired secondhand), then originality would lie rather in the devising of pertinent or fundamental questions and of the means through which unequivocal answers can be obtained.[12]

How does Addison measure up from this the latter standpoint? His question was, What is the origin of the cells that replenish the tissues in the nutritive process and appear in large numbers locally in the inflammatory process? The question rested on a body of received opinion. Addison's answer, essentially that of the corpuscular theorists before him, was novel only in that he substituted the white blood cell for a corpuscle of rather indeterminate nature. But because of the state of physiological science at the time Addison's answer came in conflict with a dominating doctrine, that of the blastema, in a way that the older corpuscular hypothesis had not. A certain degree of originality cannot be denied Addison on this score. Much more would be his due if he had kept to his earlier stand.

Consistency and persistency: These two related qualities are highly significant with respect to a scientist's achievements. Addison's question was an important one and the character of his answer made it crucial. If he had been endowed with more consistency and persistency he might have been the one to observe the passage of white cells through the walls of small vessels. He would then have inveighed even more strongly against the proponents of the blastema theory. And since a revision of the theory was already under way in Germany, he might have found himself in the forefront of scientific advance. All this is pure fancy, of course. What actually happened was that he weakened so greatly in his opposition to the blastema theory that he has been taken for one of its adherents.[13] With regard to the question of

Addison's consistency, it is not so much that he changed his mind (if he did) regarding the blastema theory as it is that he changed it at the wrong time, in the wrong direction, and for no apparent good reason. Virchow, Remak and others, men who had been at one time firm adherents of the blastema, were also in the course of changing their minds in the late forties and early fifties. Among their reasons was the one put forward so strongly and unequivocally by Addison in the early forties, namely that no one had ever actually seen a cell or nucleus take form in the blastema. Addison then began to lose sight of his original problem, and as we follow him into the fifties and sixties its outlines grow more and more hazy.

Contemporaneity: On the scale indicated by this term we can measure the degree to which an investigator is *au courant* with the best scientific knowledge of his time. Addison receives a mixed score. He at first professed an up-dated version of an outmoded hypothesis and was able to do so largely because he accepted an equally outmoded notion of the structure of capillary walls. On the other hand, he was among the first of a group of investigators who directed attention toward those little-understood cells, the white blood corpuscles. In a sense he was ahead of his time in rejecting the blastema theory, but it is obvious that this statement can be accepted only with great reservation. As for his grasp of the scientific literature early in his career, it appears good enough, suffering only when compared with that of academic scientists such as Wharton Jones, Paget, Nasse and others. Later, during the eighteen fifties and sixties, Addison's published work dropped further and further below the rising level of experimental scientific medicine. Nevertheless he remained a respected practitioner, one who, in his youth, had engaged actively and not without some success in the concerted effort to understand the behaviour and significance of the white blood cells.

1. See Appendix A for comment on Addison's published work other than that discussed elsewhere in this monograph.
2. Addison, *Actual Process of Nutrition*, op. cit., p. viii, states that the 'accumulation of the colourless blood corpuscles in the capillary vessels in the web of the frog's foot after immersion in warm water, their adhesion to the walls of the vessels, and their situation, first between the red current, and then among the fibres of the latter, is a *glaring instance* of the process of nutrition'. Addison also claims at this point that the 'views and theories hereafter set forth are deduced from these Baconian *glaring instances*'.
3. Thomas Fowler, *Bacon's Novum Organon*, edited with an introduction and notes by Thomas Fowler, Oxford, 1878. *Instantiae elucescentiae* are dealt with in Book II/24, where they are also called *instantias liberatas et praedominantes*. They are characterized as follows: 'Eae sunt, quae ostendunt naturam inquisitam nudam et substantivam, atque etiam in exaltatione sua aut summo gradu potentiae suae' (op. cit., p. 413; Fowler notes on the same page that such instances are commonly termed 'glaring'). Whether Bacon's subsequent procedure ought to be called hypothetical is open to question. In any event what he does is to draw from tables of appropriate instances conclusions regarding the 'form' or 'nature' under investigation. In the case of heat, for example, he concludes that its 'nature' is that of movement. Thereby he arrives at a 'forma sive definitio vera', namely that heat is an expansive movement: 'calor est motus expansivus, cohibitus et nitens per partes minores' (ibid., pp. 397, 404).
4. (a) I have not found any comment by Addison on the analogy drawn by Schwann between inorganic crystallization and the formation of cells in the cytoblastema. For Martin Barry's comment on this subject see Ch. II.1, note 19.

   (b) Addison's second and third 'glaring instances' are also to be found on p. viii of the *Actual Process of Nutrition*: 'The coagulation of the buffy coat of the blood is a *glaring instance* of an elastic, compact, fibrous, and colourless tissue, resulting from the fibrillation and incorporation of the colourless elements of the blood: the experiment related (p. 4) in the following chapter is a *glaring instance* of the actual formation of this tissue, in which we see how the colourless blood corpuscles and the molecules are included in the incorporated with the fibres.'

   (c) Metchnikov's rose-thorn surrounded by wandering amoeboid cells in the tissues of the larval starfish might be regarded as a Baconian glaring instance, but (in contrast to Addison) Metchnikov's hypothesis preceded his observation.
5. Cf. Ch. II.2.
6. Addison, *Law of Morphology or Metamorphosis of the Textures*, op. cit., p. 591.

7. Ibid. Here Addison cites Sir John Herschel's *Discourse on the Study of Natural Philosophy*, in which, among other topics, the Baconian classification of instances is discussed at length and an example of a glaring instance given (new edition, London, 1851, p. 193). Commenting on conflict between rival theories and taking as his two examples heat as a form of motion versus heat as a material fluid, and the particle theory versus the wave theory of light, Herschel writes: 'Now are we to be deferred from framing hypotheses and constructing theories, because we meet with such dilemmas and find ourselves frequently beyond our depths? Undoubtedly not. *Est quodam prodire tenus si non datur ultra.* Hypotheses, with respect to theories, are what presumed proximate causes are with respect to particular inductions: they afford us motives for searching into analogies; grounds of citation to bring before us all the cases which seem to bear upon them for examination' (op. cit., p. 196). Herschel's estimate of Bacon represents one extreme. He writes that before the 'publication of the *Novum Organum* of Bacon, natural philosophy in any legitimate and extensive sense of the word, could hardly be said to exist' (ibid., p. 203). William Harvey's low opinion of Bacon, as reported by Aubrey, is representative of the other. Harvey's short essay, 'Of the Manner and Order of Acquiring Knowledge', with which he introduced his *De generatione*, is thoroughly Aristotelian in outlook and says not a word of Bacon's methodology of science. For some brief comments on Harvey's essay see *Disease, Life and Man*, op. cit., pp. 2–6. In a recent assessment of Herschel's methodology C. J. Ducasse agrees with a previously expressed opinion that Herschel's book on the subject represents the first attempt by a scientist to make the methods of science explicit. (*Theories of Scientific Method: The Renaissance Through the Nineteenth Century*, Seattle, 1960, pp. 153–82.) Perhaps Harvey's essay is too short to be accorded this honour, but it is certainly worth taking into account.
8. Rudolf Virchow, 'Ueber die Standpunkte in der wissenschaftlichen Medicin', *Arch. path. Anat. Physiol. klin. Med.*, 1847, **1**, 3–19. Translated in *Disease, Life and Man*, op. cit.
9. Virchow, 'Wissenschaftliche Methode und therapeutische Standpunkte', ibid., 1849, **2**, 3–37. Translated in *Disease, Life and Man*, op. cit. Virchow states here that Bacon 'for the first time . . . after a long period of speculation, taught the scientific method. . . . It is a method which differentiates the Harveys, the Hallers, the Bells, the Magendies and the Müllers from their lesser contemporaries'.
10. Claude Bernard. *Introduction à l'Étude de la Médecine expérimentale*, Paris, 1865. In the translation by J. C. Greene (New York, 1949) the passage occurs on p. 23.
11. Some biographical information might be helpful here.
12. Karl Popper has pointed out that the most important source of our knowledge (and ignorance) is tradition, what we have read and what we have

heard (*Conjectures and Refutations*, New York, 1965, p. 27). 'A scientist,' he writes elsewhere, 'whether a theorist or experimenter, puts forward statements, or systems of statement, and tests them step by step . . . he constructs hypotheses, or systems of theories and tests them against experience by observation and experiment' (*Logic of Scientific Discovery*, rev. ed., New York, 1959, reprinted New York, 1965, p. 27). More simply, 'the work of the scientist consists in putting forward and testing theories' (ibid., p. 37). Popper's chief contribution to the methodology of science is his 'falsifiability criterion', which serves to demarcate metaphysical from scientific hypotheses and theories (ibid., *passim*). An hypothesis, in Popper's sense, can never be fully verified; it can only be corroborated. The mark of a scientific hypothesis is that it can be completely falsified by a single reliable (and usually repeatable) observation. Metaphysical hypotheses are those that can under no conceivable set of circumstances be falsified. It is interesting to consider Virchow's dictum *omnis cellula a cellula* from this standpoint (although strictly speaking, it is a generalization or prediction rather than an explanatory hypothesis). Clearly the dictum can never be fully verified. But on the other hand a single, fully recorded instance to the contrary would falsify it (cf. Appendix B).

13. W. H. McMenemy, 'Cellular Pathology With Special Reference to the Influence of Virchow's Teachings on Medical Thought and Practice', in *Medicine and Science in the 1860s*, ed. by F. N. L. Poynter, London, 1968. Professor McMenemy remarks in this informative essay that the Addison of *Cell Therapeutics* accepted the cell theory 'at any rate in principle, because he appears at that time to have been a believer in the blastema viewpoint' (op. cit., p. 25).

Appendix A

Addison's Other Publications

Medical Psychosomatism in Addison, Bennett and Virchow

The British Museum catalogue of printed books lists several works by William Addison in addition to those with which we have already become acquainted: (1) *A Dissertation on the Nature and Properties of the Malvern Water, and an Enquiry into the Causes and Treatment of Scrofulous Diseases and Consumption; Together With Some Remarks upon the Influence of the Terrestrial Radiation of Caloric on Local Salubrity*, pp. viii, 192, 8°, London, Callow Wilson, 1828; (2) *A Letter to William Lawrence . . . on the Nature and Causes of Intellectual Life and the Mind*, pp. 35, 8°, London, T. and G. Underwood, 1830; (3) *Practical Suggestions for Ameliorating the Present System of Affording Medical Relief to Paupers, etc.*, pp. 24, 8°, London, James Ridgway & Sons, 1837.

The first of these works, a treatise of considerable size on the salubrious features of Addison's homeland, a hilly region lying about 120 miles northwest of London, is of interest here only insofar as it directs our attention toward a perennial feature of Western medicine, namely the belief in the healing virtues of airs, waters and places. Medical interest in this topic can be traced back at least as far as the Hippocratic writings (*Peri Aerōn, Hydatōn, Topōn*, On Airs, Waters, Places, in Hippocrates, trans. by W. H. S. Jones, London, 1957, vol. 1, pp. 70–137). The strength of the tradition is nicely indicated by the statement that Malvern's 'modern fame rests on its fine situation, pure air, and chalybeate and bituminous springs' (*Encyclopaedia Britannica*, art. 'Malvern', 11th ed., 1910–11). For centuries, if not millennia, one of the chief therapeutic measures available to the physician (in the tradition of Hippocratic medicine) has

been the dispatch of his patient to the 'place' most appropriate for recovery, that well-known 'change of air' rationalized in so many ways. Until the nineteenth century systematic medical treatises dealt with a standard list of six factors that both determined the state of health or illness of the patient and were at the same time to some degree manageable by the physician. These six factors (bearing the curious designation of 'non-naturals') are, respectively: air, food and drink, sleep and watch, motion and rest, evacuation and repletion of the body, and the emotions or 'passions' of the mind. Under the heading of 'air' fell in addition all salutary and non-salutary aspects of climate, season and place (cf. L. J. Rather, 'The "Six Things Non-Natural": a note on the origins and fate of a doctrine and a phrase', *Clio Medica*, 1968, **3**, 337–47).

The second of Addison's works listed above indicates his early concern with the psychosomatic aspect of human existence. In it he seems to adopt a trialistic, rather than a dualistic, stance: 'The body I consider as a machine living organically, or performing certain functions by the impulse of some agent, very different from that principle in which the consciousness of a capacity to know exists' (op. cit., p. 4). This remark recalls the tripartite soul or powers thereof found in Plato and Aristotle rather than the straightforward dualism of Descartes. Addison's few comments here on the subject are probably not worth prolonged analysis. I shall only point out that his interest in the emotional, 'psychosomatic', side of human disease was quite in line with the long-standing official interest of physicians in the sixth of the 'non-naturals', the emotions or passions of the mind.

While philosophers racked their brains from the seventeenth century onward to explain how 'mind' could affect 'body' and yet leave the laws of physical mechanics intact, physicians by and large simply accepted what they regarded as the evidence of everyday experience, namely that the emotions or passions did in fact have strong effects on the human body and that these effects had to be taken into account in respect to the cause and cure of human disease

(for literature cf. L. J. Rather, *Mind and Body in Eighteenth Century Medicine, A Study Based on Jerome Gaub's 'De regimine mentis'*, Berkeley, Los Angeles and London, 1965). Addison was no exception. Scattered throughout his writings are passages in which the effect of 'mind' on physiological processes is taken for granted. In 1844, for example, we find him stating, without preliminaries, that 'if imagination, mind and mental emotion, can vary the process of nutrition, and retard or accelerate a secretion, they can also vary the qualities of the blood-fluid and therefore of the urine' ('On the fluid elements of the circulating blood, and on the constant changes and variation to which it is liable', *Prov. med. surg. J.*, 31 July 1844, p. 266), where the implication, clearly, is that 'mind' can do all these things.

A somewhat longer passage in Addison's writings, indicative of the way in which nutritive or inflammatory processes may be affected by the emotions, runs as follows: 'We know that various impressions on the organism, mental emotions, fear, anger, etc. powerfully affect the circulating current of the blood, and that torrents of cells, in obedience to some law, rush here or there, suddenly distending the capillaries of the face and neck. We know that these phenomena are accompanied by various disturbed sensations, by accelerations of the pulse, sickness, faintness, etc. (*Actual Process of Nutrition*, second part, op. cit., London, 1845, p. 95); for somewhat similar remarks by William Harvey cf. L. J. Rather, 'Old and new views of the emotions and bodily changes: Wright and Harvey versus Descartes, James and Cannon', *Clio Medica*, 1965, 1, 1–25. And, twenty-three years later, we find Addison stating that 'great restlessness like a strong emotion tends to increase disorder of the blood, and thereby influences an inflammation, altering it from common to specific' (*Co-Existence of Two Species of Inflammation*, op. cit., London, 1868, p. 25).

Addison's statement that strong emotions may adversely affect the inflammatory process and that the power of the imagination may affect nutritive and secretory processes can easily be matched with similar statements, based on medical

experience, in writers from the time of Galen down to the nineteenth century (cf. *Mind and Body in Eighteenth Century Medicine*, op. cit., *passim*). A single and especially pertinent example, drawn from Rudolf Virchow (hardly a man famous for his involvement in psychosomatic currents of thought) may suffice. In discussing the effects of the blockage of sebaceous gland ducts associated with hair follicles, Virchow comments that nothing more serious than simple nutritional atrophy of the gland may result. But, he continues: 'A more significant and persistent disturbance, be it of physical or mental character, in that it brings about a hastening of the circulation, in particular perhaps a simple hyperaemia of the skin, a sojourn in heated air even, a febrile condition, in short any cause able to heighten the circulation of the skin, can transform that simple nutritional disturbance into an inflammatory one: a restless night, an evening passed in dancing, suffice to produce a focus of inflammation in the neighbourhood of the dilated hair follicle' (*Handbuch der spec. Path. u. Therapie*, op. cit., vol. 1, p. 78). (The reader may be interested in comparing the foregoing remarks by Addison and Virchow with those of a modern microbiologist and epidemiologist, René Dubos, in his *Mirage of Health*, esp. chapters IV and VI.)

One chapter of Addison's book, *On Healthy and Diseased Structure*, is devoted to what he terms 'practical psychology' (op. cit., pp. 85–130). Here he adopts a modified dualistic view of the nature of man. The human being is, he writes, both 'an individual possessing a conscious unity' and 'a living being . . . subject to the laws of matter'. The physician must bear this in mind in the treatment of patients, for, 'if, as in the practice of medicine, we be required to assuage a pain, alter a sensation, and stop the progress of disease—we must, to the utmost extent, analyse the phenomena of life in a twofold—a somatic and psychological point of view. . . .' Addison then subdivides the realm of the somatic into (a) the 'inorganic' (cohesion, crystallization, chemical affinities) and (b) the 'vegetable' or 'morphological' (growth, nutrition, reproduction and secretion); and

the realm of the psyche into (a) 'temperament' or 'neurological' (sensual perception, emotions and emotional movements) and (b) 'mind' (thoughts and moral sentiments). He continues: 'If, therefore, we grant that human nature is susceptible of the quadripartite consideration, which we have endeavoured to illustrate and establish—inorganic, morphological, sensual and intellectual; and if, moreover, we trace in man's bodily structure, organs appropriate to each;—then we must be prepared to carry out these principles into the domain of diseases and cures. . . .' The physician, says Addison, knows that external agents, such as air, water, food, climate, light and heat, are 'necessary to the life of man, and they are also causes or conditions of disorder and disease; so the inward psychological agent is necessary to the phenomena of life, and also influential in producing disturbances and disease'. After thus giving a general statement of the doctrine of the non-naturals (in barely disguised form) Addison turns to its specific relevance in regard to 'consumption', the disease that occupied so much of his attention and for the cure of which the region of Malvern was famed. 'That which is true universally,' he writes, 'is of course true in particular instances, and therefore, in the treatment of particular diseases, and in our efforts to cure consumption, we frequently find the best endeavours opposed by unfavourable external conditions we cannot alter; by irritating emotions we cannot quell; and mental anxieties we cannot remove. In large and populous cities, where multitudes of persons live crowded together in wretched habitations, following unhealthy occupations, with insufficient food, an impure atmosphere, and bad water, health is at a low standard, and the mortality is excessive. For the sickness and mortality above the natural average the physician knows the cure, but it is beyond his power to employ or enforce the remedy. He cannot feed the hungry, purify the atmosphere, or clothe the naked, nor alter the social position of his patient so as to admit of change of situation. It is in these instances that unfavourable external conditions cut at the root of infant life, deteriorate the morphology of struc-

ture, and produce a dire amount of inflammatory and scrofulous disease.'

Finally, a brief look at Lecture XII of John Hughes Bennett's Lectures on Molecular Physiology, Pathology and Therapeutics (op. cit., *Lancet*, 12 December 1863). Bennett was clearly fascinated by the technique of therapeutic hypnotic suggestion. In reference to a brilliant cure by James Braid of hysterical paralysis of several years standing in a young woman, Bennett remarks that in his opinion 'cases of this kind constitute one of the great therapeutic advancements of modern times, being not only directly applicable to the cure of maladies, but indicating a most important principle explanatory of innumerable recoveries hitherto too much neglected by the medical profession' (op. cit., p. 671). In regard to the 'influence which the Mind exerts over the Body' Bennett had this to say: 'Thus, although it is universally known that mental emotions exercise a stimulating or depressing effect on all the bodily functions, and that various feelings, desires, and appetites increase or diminish the secretion of different glands, it has been reserved for modern times to demonstrate that in certain persons sensation and volition can be thoroughly controlled by the suggestive ideas of another individual' (ibid.). We see that Addison, Virchow and Bennett, however much they differed on other points, shared some measure of agreement regarding the importance of psychosomatic factors in the cause and cure of bodily disease.

Appendix B

Early Attempts to Distinguish Various Kinds of White Blood Cells

Ehrlich's *Farbenanalyse*

All studies on blood cells so far referred to were made on unstained and, for the most part, living specimens. Max Schultze's paper of 1865 shows the full extent of the advantages and limitations of this method. ('Ein heizbarer Objekttisch und seine Verwendung bei Untersuchungen des Blutes', *Archiv. mikr. Anat.*, 1865, 1, 1–42.) Schultze introduced the use of a microscope stage heated to 35–40°C. by an alcohol flame and this he combined with von Recklinghausen's moist chamber technique so as to carry out studies of mammalian blood cells in thin fluid films at body temperature. At such temperature, Schultze found, the 'creeping' movements of the white or colourless blood cells were very lively, so much so as to resemble 'those of ordinary free-living amoebae'. Schultze referred back to Wharton Jones' distinction of finely and coarsely granulated forms of white cells, made in 1846, and then introduced his own classification. He distinguished (1) white cells as small as 0·005 mm. in diameter but usually about the size of red cells, containing a single large nucleus and a scanty rim of protoplasm and devoid of granules; (2) slightly larger cells with similar nuclei, their protoplasm containing a few fine granules; (3) 'typical white blood cells', 0·009–0·012 mm. in diameter, containing one, two or three nuclei often visible with difficulty and surrounded by protoplasm in which numerous very fine granules could be seen (displaying no 'molecular movements' under ordinary conditions); and (4) the coarsely granulated cells of Wharton Jones, similar to the finely granulated cells in all other respects and much easier to follow, because of their highly visible, refractile

granules. The cells of classes (1) and (2) were only slightly 'amoeboid'; at best they occasionally threw out and withdrew protoplasmic extensions. The cells of classes (3) and (4) moved about rapidly and freely. They ingested particles (up to 0·003 mm in diameter) of milk, indigo, aniline blue and carmine introduced into the fluid suspension. The coarsely granulated cells engaged in this activity—termed by Schultze 'feeding'—at a somewhat slower pace. Schultze did most of his work on animals, but on one occasion he examined the blood of a human patient and found it to contain a very large number of white cells of the finely granulated variety. Schultze's drawings very nicely illustrate his findings.

So much for the observation of living, unstained cells in fluid films of blood examined under the microscope. It is fair to say that little or nothing remained to be learned from this procedure and that in consequence a dead end had been reached by the seventies, out of which Paul Ehrlich was to point the way. His first paper on the subject, 'Contributions to the Knowledge of Aniline Dyes and their Application in Microscopical Technique', appeared in 1877. Ehrlich was at the time a twenty-three-year-old medical student at Freiburg. He noted in this paper that while aniline dyes had found wide use in the textile industry they had been neglected by microscopists engaged in the study of animal tissues, even though the histologist was in a better position to make good use of them than the dyer of textiles. Ehrlich was familiar with methyl violet as a stain for deposit of amyloid in the tissues (as introduced, he writes, by Cornil and by Jurgens and Heschl) and with Zuppinger's use of aniline blue (triphenylrosaniline) to stain axis cylinders and dendritic processes of nerve cells. Ehrlich himself used Dahlia (monophenylrosanilin), a purplish dye tried and rejected for his own purposes by Zuppinger, to stain selectively the 'protoplasm' (our 'cytoplasm') of certain cells widely distributed throughout the body. These he identified with the coarsely granular 'plasma cells' that Waldeyer had described a few years before and regarded as

embryonal cells distributed throughout the connective tissues and certain organs. By staining his sections in neutral, watery solutions of Dahlia and then de-colourizing them with acetic acid under controlled conditions, Ehrlich was able to colour selectively the specific granules of the 'plasma cells' (our 'basophiles' or 'mast cells'). The granules took an off-shade nuance of the original dye colour. They were insoluble in alcohol and ether (hence not composed of fat) and could be more or less selectively stained with other aniline dyes (primula, iodine violet, saffranin, fuchsin). The essence of Ehrlich's staining procedure is made evident in his first paper. As one of his pupils later wrote, Ehrlich's aim was not to maximize the effect of a stain on cells and tissues or to search for general purpose stains (such as the now familiar hematoxylin and eosin preparation in which nuclei are blue and everything else a shade of reddish pink). It was to find selective stains and maximize their selectivity by controlled de-colourization. This was his 'principle of maximal decolourization'. In 1878 Ehrlich termed his procedure 'colour analysis' (*Farbenanalyse*). Unlike a chemical reaction carried out under the microscope between (a) a known chemical substance already present in cells and tissues, (b) one added by the investigator to yield and (c) a coloured substance of known chemical constitution (microscopic histochemical analysis), Ehrlich's colour analysis simply attempts to identify a visible structural component by imparting to it a specific colour, the details of the chemical or physical reaction between structural component and dye being as a rule poorly or not at all understood and in any case beside the point. Where histochemical analysis aims at chemical identification, colour analysis aims at structural identification.

Ehrlich took his medical degree at Leipzig in 1878 and went immediately to the Charité hospital in Berlin. In his first paper delivered there he returned to the granulated 'plasma cells' of Waldeyer and rejected most of what had been said about them, including their supposed embryonal character. They appeared, he said, in the connective tissues

in increased number as an accompaniment of chronic inflammatory processes, and in general were more numerous wherever tissue nutrition was undergoing increase. They could therefore be regarded as products of the fattening or overfeeding (*Mästung*) of connective tissue cells. He suggested therefore that they be called 'mast cells' (*Mastzellen*). Their granules took an off-shade when stained with basic aniline dyes. Ehrlich later included the basophile granulated white cells of the blood in this group. In his second paper of the same year, 'On the Specific Granules of the Blood', Ehrlich limits the term 'granule' to bodies present within cells during life, whether composed of fat or protein. (Ehrlich also became interested in the staining characteristics of cells found in the spleen and bone marrow, due to the discovery in the late sixties, made independently and almost simultaneously by Ernst Neumann in Germany and Giulio Bizzozero in Italy, that the bone marrow was a source of blood cells. As for the spleen it had, together with the lymph glands, long been regarded in this light.) Ehrlich at first divided the cell granules into three groups designated alpha, beta and epsilon, but in his definitive paper of 1880 he dropped the last group (or at least did not mention it) and introduced a new 'gamma' group together with the terms 'acidophil', 'basophil' and 'neutrophil', still current for the granules and the cells containing them. Aniline dyes, he pointed out, could be classified as basic or acidic, the former representing coloured 'basic' radicals combined with hydroxyl ions, the latter coloured 'acidic' radicals combined with hydrogen ions. The alpha granules of certain leucocytes avidly combined with acid dyes, such as eosin, bengalin and nigrosin, hence they could be called acidophilic granules (sometimes 'eosinophilic', since this stain was so widely used). The gamma granules were basophilic, combining with such dyes as fuchsin, safranin and Bismarck brown. But most of the circulating leucocytes contained neither one of these two classes of granules. Instead they bore very fine granules with a strong chemical affinity toward the combinations of coloured bases with

coloured acids (e.g. picric acid-rosaniline) that Ehrlich designated 'neutral' dyes, hence 'neutrophilic' granules. The cells containing neutrophilic granules fell into two classes, one the class of the most numerous white cells in the blood, characterized by a lobated 'polymorphous' nucleus ('polynuclear' was Ehrlich's term) the other that of the less numerous large mononuclear cells, whose extra-nuclear protoplasm was sparsely dotted by neutrophile granules. Ehrlich pointed out that haemoglobin was neither acidophilic nor eosinophilic, although its native colour had in 1879 deceived both Hayem and Pouchet in France into mistaking certain cells in the blood (identified by Ehrlich with his eosinophil leucocytes) for 'leucocytes à grosses granules de substance hémoglobinique'.

With the aid of the distinctions between cells drawn by Ehrlich's method of colour analysis and the demonstration of the source in the bone marrow of the innumerable leucocytes that, in the form of 'pus corpuscles', jammed the tissues and filled body cavities in the course of acute inflammation, a new field of study was opened. Ehrlich himself stated that while the importance in pathology of the circulating leucocytes rested chiefly on Virchow's description of leukaemia and Cohnheim's doctrine of emigration his own tinctorial techniques now permitted investigators to move forward from the resting point where, in the words of Rindfleisch, the 'leucocyte' had represented 'a kind of omnibus in which everything imaginable travelled'. The leucocytes or colourless corpuscles, whether circulating in the blood or moving about like amoebae in the tissues, were now classified as (1) lymphocytes, with large, round single nuclei and scanty rims of protoplasm, (2) large mononuclears with round or oval nuclei and abundant extranuclear protoplasm, (3) cells resembling those of class 2 except for indentations in their nuclei, (4) neutrophilic and acidophilic polynuclear leucocytes, these last two making up together about 75 per cent of the white cells in the circulating blood. Basophiles amounted to less than one out of a hundred of the white cells present in the blood under normal circumstances.

Since Ehrlich's procedure was to count as few as one hundred white cells at random in stained smears and express the differential results in percentages the basophiles, by an accident of counting, seemed to be hardly present at all, whereas their absolute number in the circulating blood was of course in the hundreds of millions. Ehrlich's collected papers are conveniently available in his *Farbenanalytische Untersuchungen zur Histologie und Klinik des Blutes*, Leipzig, 1891.

It might be supposed that another technical advance of the eighteen seventies, the design and theory of high-power apochromatic lenses and improved methods of illumination, should have contributed much to the advance of normal and abnormal histology. In fact, the newly available equipment contributed very little. The advantages of the achromatic objectives corrected for spherical aberration and the means of artificial illumination introduced in the 1830s had been very real in serving, for example, to eliminate as optical artifacts some of the innumerable granules and spherules seen by microscopists previously. The use of thin sections of tissue, mounted in transparent media under thin glass coverslips (such coverslips were available commercially by the mid-century), and of stained dried films increased the amount of work done with the higher power immersion objectives, but at best linear magnification was merely doubled. This could be helpful in occasional instances. Ehrlich, for example, remarks that the neutral or epsilon granules of stained leucocytes are visible only under the highest power oil-immersion lenses. Due to their refractility in the unstained state however, these same granules had long since been seen in living polymorphonuclear leucocytes, where they filled the cell body. Even the occasional epsilon granules present in large mononuclear cells seem to have been discerned by Schultze before Ehrlich. The limits of optical resolution and therefore of useful magnification were reached in the eighties and these limits were so close to the older ones that no new world of dimensions was opened to the scrutiny of the microscopist.

Appendix C

Subsequent Fate of the Blastema Theory in England, France, Germany and the U.S.S.R.

That the blood is a living substance and the seat of life is a belief held in the past by many peoples, among them the Hebrews and the Greeks. William Harvey pointed out the antiquity of this doctrine while adopting it himself in 1651 on the basis of his studies of the chick embryo: '. . . life, therefore, resides in the blood (as we are also informed in our sacred writings) . . . blood is the generative part, the fountain of life, the first to live, the last to die, and the primary seat of the soul . . .' ('Anatomical Exercises on the Generation of Animals', in *The Works of William Harvey*, trans. by Robert Willis, London, 1847, pp. 376, 377). Harvey then cites Aristotle, Diogenes, Heraclitus and Alcmeon on the subject. A little more than one hundred years afterwards John Hunter, one of the founders of nineteenth-century blastema theory, cited both Harvey and Aristotle in support of his own claim (based in large part on his studies of the healing of wounds and fractures) that the blood, although a fluid, was endowed with life (Hunter, ed. by J. F. Palmer, op. cit., p. 105). According to Hunter the chief formative substance of the blood, the 'coagulating lymph' (corresponding to the fibrinous coagulum of shed blood) is extravasated from blood-vessels wherever there is need for growth or repair of parts (ibid., pp. 119, 120). The 'blastema' or 'plasma' of nineteenth-century biological theorists is, in essence, Hunter's 'coagulating lymph', as indeed most of them knew.

Schwann's cell theory was in the tradition of Harvey and Hunter to the extent that a 'formless' living substance was ontically prior to 'formed' structures. For Harvey and Hunter the structural elements were, presumably, 'fibres';

for Schwann they were cells. Once formed, the cells were, according to Schwann, the source of all subsequent structural transformations. But the new cell theory, professed by Remak, Virchow and others from the eighteen fifties on, made the cells primary. Cells were no longer derived from an amorphous living substance, the 'cytoblastema'; cells were, rather, the sole source of other cells. The blastema theory did not disappear at once from the scene with the advent of Virchow's *omnis cellula a cellula*, continuing instead to flourish for somewhat longer than is usually recognized by historians of science. It then went underground in the latter part of the nineteenth century and almost disappeared from sight. It surfaced again in the middle of the twentieth century. Only a few aspects of the matter will be presented in the following paragraphs; the subject as a whole is too large for systematic treatment here.

John Hughes Bennett, the old rival of Addison and Virchow, attempted to refute Virchow's cellular pathology and the cell theory on which it was based in his own 'Lectures on molecular physiology, pathology and therapeutics' (*Lancet*, 1863, 3 January, pp. 1–4; 17 January, pp. 55–57; 7 February, pp. 139–41; 21 February, pp. 199–202; 7 March, pp. 259–62; 4 April, pp. 378–81; 25 April, pp. 459–61; 30 May, pp. 597–600; 4 July, pp. 3–6; 29 August, pp. 239–42; 5 December, pp. 643–46; 12 December, pp. 671–75). The 'molecules' referred to in the title are of course those of the histologist: Bennett states that we 'must substitute for the hypothetical atoms of the chemist the visible molecules of the histologist, and demonstrate how all researches and discovery in recent times tend to support a molecular rather than a cellular theory of organization' (op. cit., 3 January, p. 1). He then admits that a 'cell, once formed, may produce other cells by buds, by proliferation, or by division', but that on the whole new cells arise from 'histogenetic' molecules (ibid., p. 3). The belief that tissues originate from cells alone is, in Bennett's opinion, a fallacy. This view 'asserts that all embryonic textures in the ovum, all adult tissues during life, and every kind of morbid formation,

are to be traced to the cell and can originate in it alone . . . parodying the celebrated saying of Harvey, *omne animal ex ovo*, it has been attempted by Virchow to establish the law of *omnis cellula e cellula* . . . such a doctrine is inconsistent with the facts, and we shall see that histologists (including Virchow himself) have been unsuccessful in tracing all tissues back to cells, that they have universally recognized that cells must originate in the first instance from a formless or molecular fluid, called by Schwann a blastema' (op. cit., pp. 191–202). Tumours, also, cannot be explained by the new cell theory; they are in fact propagated not by cells but by a 'molecular fluid'. Bennett writes in this connexion: 'Professor Virchow has recently maintained that all growths, including pus, cancer and even tubercle, originate by the endogenous growth of previously existing cells . . . but that they all do so, and that morbid growths can be formed in no other way but from cells we have seen to be erroneous' (op. cit., p. 241). An interesting sidelight is Bennett's opinion that a 'molecular theory of germs' is required in order to account for communicable fevers. These 'germs' are effective by virtue of 'molecular action . . . analogous to that of a ferment' (op. cit., p. 461).

It should not be supposed that Bennett's views were simply the result of his long-standing anatagonism to Virchow. They were shared by others. William Turner, Senior Demonstrator of Anatomy at the University of Edinburgh, for example, remarked in 1863 that, 'though banished from the field of normal histogenesis, the mode of origin of cells in a fluid blastema by a free spontaneous generation, is still considered by some to be the one which prevails in pathological cell-formations; and the well-known inflammatory exudation-corpuscles, and the cells of pus, cancer and tubercle are regarded as produced in this manner . . . the exudation, which is not unfrequently poured out from the blood-vessels amongst the textures, is looked upon as the equivalent of that fluid blastema in which Schwann supposed the spontaneous cell-formation to occur in the course of normal development' ('On the present aspect of

the doctrine of cellular pathology', *Edinb. med. J.*, 1863, 8, 873–97; cf. p. 875). After reviewing the evidence Turner was able to make no stronger a statement in favour of Virchow's cellular pathology than that 'the doctrine, that pathological cell-formations arise from pre-existing textural elements [i.e. cells] has not been founded on insufficient data' (ibid., p. 897). Turner, incidentally, noted that Schleiden, 'usually considered as a supporter of the theory of free cell-formation', in fact 'fully recognized that the new cells of plants were never formed except within those already existing' (ibid., p. 875; cf. also Ch. III.1, note 7). Again, when Charles Darwin turned his attention to the matter in 1868 he noted that 'Virchow, the great supporter of the cellular theory, whilst allowing that difficulties exist, maintains that every atom of tissue is derived from cells, and these from pre-existing cells, and these primarily from the egg, which he regards as a great cell. . . . Another school maintains that cells and tissues of all kinds may be formed independently of pre-existing cells from plastic lymph or blastema; and this is thought well exhibited in the repair of wounds.' Darwin's modest conclusion was that since he had no special competence in the matter 'it would be presumptuous in me to express an opinion of the two opposed doctrines' (*The Variation of Animals and Plants Under Domestication*, London, 1868, 2 vols., vol. 2, p. 370). Darwin thought it safer to use instead of 'cell' the term 'organic unit' of E. Montgomery (cited on p. 370 by Darwin as the author of *On the Formation of So-Called Cells in Animal Bodies*, 1867, in which the formation of cells from other cells was denied; for Huxley's two views see Ch. III.1, note 10).

The supposed mode of formation of new cells in morbid exudates continued to be the last stronghold of the blastema theory. In France we find Charles Robin writing in 1874 that the 'mediate condition of suppuration is a disturbance of the capillary circulation, and the immediate condition is the production of a blastema with the aid and at the expense of which the genesis of leucocytes takes place'. While Robin makes allowance also for the escape of leucocytes from

blood-vessels, he says that they mingle with the 'newly generated leucocytes'. And in the case of non-vascular tissues all leucocytes arise from extruded blastema (*Leçons sur les Humeurs normales et morbides du Corps de l'Homme*, Paris, 1874, pp. 378–83, *passim*). In Germany one of Virchow's former pupils, Paul Grawitz, pointed out that even if the origin of cells from pre-existing cells were to be verified for the millionth time his own doctrine that another mode of origin was possible as well would remain unaffected (*Atlas der pathologischen Gewebelehre*, Berlin, 1893, p. 12). Grawitz compared himself to a gardener who had accepted the dictum 'omnis arbor e semine' until he discovered one day that trees could be propagated from slips. Speaking less figuratively, he had convinced himself, on the basis of microscopic observations, that the so-called 'ground-substance' (*Grundsubstanz* of Virchow and others) lying between connective tissue cells and fibres was capable, under certain circumstances, of giving rise to cells. 'The ground-substance derived from cells,' he writes, 'so long as it lives and takes part in metabolic interchange, is capable of returning to the cellular state' (ibid., p. 13). In writing that the ground-substance contained 'living substance' Grawitz borrowed the English phrase from C. Heitzmann, who was an opponent of the cell doctrine in its entirety, somewhat in the manner of the early Huxley (Grawitz, op. cit., p. 13; C. Heitzmann, *Microscopical Morphology of the Animal Body in Health and Disease*, New York, 1883; cf. pp. 57–58). For Virchow's opinion of the work of Grawitz and Heitzmann see his *Hundert Jahre allgemeiner Pathologie*, Berlin, 1895; translated in *Disease, Life and Man, Selected Essays by Rudolf Virchow*, Stanford, 1958; cf. pp. 203, 204. The observations on which Grawitz based his claim that nucleated cells arose from the amorphous or finely granular 'ground-substance' of the connective tissues during the inflammatory process cannot occupy us here, but it should be said that they have puzzled many light-microscopists since.

Grawitz found few who were willing to take his claims seriously, the more so since the details of indirect cell

division—so-called 'mitotic' division—had been worked out by Walther Flemming and others in the eighteen seventies. Cells and nuclei had at first been thought to divide 'directly', i.e. by simple constriction. In 1857 Virchow amplified what was generally known as Remak's scheme of cell division to hold that first the nucleolus, then the nucleus and finally the cell body underwent local constriction and subsequent division ('Ueber die Theilung der Zellkerne', *Arch. path. Anat. Physiol. klin. Med.*, 1857, **11**, 89–91). This account was then taken up by writers of textbooks of histology, physiology and pathological anatomy. In Flemming's definitive monograph of 1879 his own findings and those of others on the subject of indirect cell division are admirably described and beautifully illustrated. Flemming worked with both living, unstained cells and fixed (dead) cells stained with aniline dyes to bring out morphological details. His drawings of chromosomal transformations as seen in the dividing nuclei of living cells could hardly be improved on today, even with the aid of phase contrast microscope objectives ('Beiträge zur Kenntnis der Zelle und ihrer Lebenserscheinungen', *Arch. mikr. Anat.*, 1879, **16**, 302–436).

Grawitz' belief that cells could arise from the living ground-substance dispersed throughout the connective tissues of the body, and his opposition to Cohnheim's explanation of the origin of cells in inflammatory exudates that went with it, was adopted by his grandson, Paul Busse-Grawitz. In the nineteen fifties, for reasons that shortly will be made plain, the latter's findings became of great interest to pathologists in Germany and were the occasion of considerable debate. In one of his papers Busse-Grawitz attempted to show how polymorphonuclear leucocytes in inflammatory fields were built up locally, in three stages, from non-cellular particles ('Beginn des Entzündungsprocesses im Bindegewebe', *Arch. path. Anat. Physiol. klin. Med.*, 1951, **321**, 62–76). He also brought forward experimental evidence purporting to prove that the leucocytes subsequently found in ectopically transplanted corneas were

not derived from the host but developed, rather, from the substance of the transplant ('Schlummerzellentheorie und Cohnheim'sche Entzündungslehre', *Zentralbl. allg. Path. path. Anat.*, 1958, **98**, 477–84). Among others, the doyen of German pathologists, Robert Rössle, came to grips with the problem in 1957. He concluded—with some reservations and admissions—that the basic premise of cellular pathology, '*cellula a cellula*,' remained intact and that the ground-substance was incapable of forming new cells ('Molekularpathologie und Cohheimsche Leukocytentheorie', *Zentralbl. allg. Path. path. Anat.*, 1957, **96**, 376–89).

Busse-Grawitz' adherence to the claim put forward by his grandfather that the amorphous ground-substance had the power of forming new cells might have attracted less attention in Germany had it not corresponded in time with the rise of a new cell theory which began to gather support in the U.S.S.R. shortly after the end of the Second World War. According to this theory, largely the work of Olga B. Lepeshinskaya, cells originated not only from the division of pre-existing cells, but from 'living substance' (*zhivovo veshchestva*) as well. Her monograph of 1945 on the subject was introduced to the English-speaking world in a book review by Professor Ovlit (*Proiskhozhdeniye kletok iz zhivovo veshchestva i rol zhivovo veshestva v organizme* (The Origin of Protoplasmic Cells and the Role of Protoplasm in the Organism), Academy of Sciences, U.S.S.R., 1945; cited from a review by Prof. Ovlit in the *American Review of Soviet Medicine*, 4, 472–74). Lepeshinskaya's experiments were said by Ovlit to have disproved the 'mechanistic theory of Virchow that "each cell arises only from another cell"' and that 'there is nothing living outside the cell' (loc. cit., p. 472). According to Ovlit, Lepeshinskaya concluded that 'although cell division cannot be denied, it is evident that each cell originates not from a cell but from protoplasm'. The preface to the monograph was contributed by Trofim D. Lysenko, who hailed Lepeshinskaya's proof of the 'origin of cells from amorphous substances'

as a great contribution to Soviet biology (Ovlit, loc. cit., p. 472).

A second edition of Lepeshinskaya's monograph on the origin of cells from living substances was published in 1950. A number of representative passages may be found in a review of the German translation (M. Brandt, 'Die Ursprung der Zellen aus lebender Substanz und die Rolle der letzteren im Organismus', *Zentralbl. allg. Path. path. Anat.*, 1952, **88**, 128–31). One such passage is particularly pertinent. Lepeshinskaya writes: 'One hundred years ago Schleiden and Schwann attempted to investigate the origins of the cell. But the majority of "reactionary bourgeois" savants, who opposed evolutionary theories and defended a position of the dogmatists, rejected their doctrine. Virchow's mechanistically and metaphysically oriented cell theory stifled the evolutionary idea of Schleiden and Schwann on the free formation of cells from the cytoblastema and ruled thereafter for more than ninety years' (loc. cit., p. 128). According to Lepeshinskaya the development of cells from 'living substance' ('protoplasm', in the English translation) takes place in three stages involving the successive formation of (1) protoplasmic spherules, arising in the 'formless mass of living substance', (2) nucleus and (3) the complete cell (ibid., p. 129). In keeping with the intellectual climate in the U.S.S.R. at the time, strongly influenced by ideological determinants that were shortly to lose their force, Lepeshinskaya wrote that her findings were in accord with those of Darwin, as further developed by Ivan Michurin and Trofim Lysenko, closing with a note of thanks to that 'greatest of all savants, Comrade Stalin' (ibid., p. 130). The ideological and political support commanded by Lepeshinskaya's work led the Moscow Society of Pathological Anatomists to issue in 1952 a critique of Virchowian cellular pathology, the 'famed dogma of Virchow that every cell arises only from another cell' being rejected as 'incorrect' (*Resolution der Moskauer Gesellschaft der pathologischen Anatomen*, 'Zur Kritik der Virchow'schen Zellularpathologie und Wege zur Entwicklung der sowjetischen

Patho-Morphologie', *Zentralbl. allg. Path. path. Anat.*, 1951, 87, 34–38; cf. p. 35). The Society also recognized Alexei Speransky's re-formulation of pathological theory in terms of early nineteenth-century 'neural pathology' as, with some reservations, 'progressive', and the members were advised to study the classic works of Marxism-Leninism (ibid., pp. 36, 37; cf. *A Basis for the Theory of Medicine*, by Alexei Speransky, trans. and ed. by A. P. Dutt, New York, 1936).

A brief comment on the political and social aspects of Virchow's biological theory of the cell may be useful at this point. We have seen Virchow defending, in terms of political metaphor, the rights of the third estate (the cells) against those of the aristocracy (the blood) and the clergy (the nervous system) (Ch. III.1). The cells constitute a 'free state' of individuals with equal rights, Virchow notes elsewhere (*Cellular-Pathologie*, op. cit., p. 25). From the standpoint of dialectical materialism however, as Friedrich Engels pointed out in 1885, the acceptance of polar opposites such as 'state' versus 'individual' or 'organism' versus 'cell' is an error generated by mechanistic, metaphysical categories of thought. Engels's comments on Virchow's concept of the cell are worth citing at length: 'If, in consequence of the discovery of the cell, Virchow was already compelled years ago, more progressively than scientifically or dialectically, to reduce the unity of animal individuality to a federation of cell-states, so the concept of animal (and therefore human) individuality becomes still further complicated by the discovery of amoeboid white blood cells creeping about in the bodies of higher animals. But it is just these mighty fixed boundaries and class differences, conceived of as irreconcilable and irreducible polar opposites, that have given modern theoretical science its limited metaphysical character' (*Herrn Eugen Dührings Umwälzung der Wissenschaft*, Vorwort zu der Auflage von 1885, Karl Marx, Friedrich Engels Werke, Berlin, 1962, vol. 20, p. 14). Engels's remark that Virchow's concept of individuality was more progressive (*fortschrittlich*) than

scientific was word-play on Virchow's role as one of the founders of the German Liberal Party (*Fortschrittspartei*) in 1861 (op. cit., p. 629). In 1962 Virchow was regarded by authorities of the German Communist Party as a 'violent opponent of socialism and a reactionary, after 1871' (op. cit., p. 725), although as recently as 1946 his 125th birthday celebration commanded an entire issue of a medical journal published in the Soviet zone of occupied Germany (*Das deutsche Gesundheitswesen*, Heft 25, 1, Berlin, 20 December 1946). This issue included a eulogy of Virchow by the chief of the department of public health of the Soviet military government (*Rudolf Virchow und der Fortschritt der Wissenschaft*, ibid., pp. 787, 788).

The political support given to Lepeshinskaya's work along with that of Lysenko and Speransky seems to have crumbled in the later nineteen fifties. At the same time various attempts made in other laboratories of the socialist world to verify the findings of Lepeshinskaya and her colleagues ended in failure. In the late fifties the 'new cell theory' was reviewed at length and found wanting by two Soviet scientists in a communication to the American journal, *Science* (On 'The new cell theory', 1958, **128**, 182–86). One of the more important pieces of biochemical evidence adduced in favour of Lepeshinskaya's theory of the cell was the claim that labelled amino acids (methionine-S^{35} and glycine-C^{14}) became incorporated into proteins of incubated blood plasma, thus apparently confirming Lepeshinskaya's belief that plasma was 'one of the variants of living substance' (op. cit., p. 183). That claim, which, incidentally, would no doubt have been warmly received by William Harvey and John Hunter—had been denied, as early as 1953, by other Soviet biochemists. Similarly, the morphological and other observational data thought to favour 'the new cell theory' (i.e. the revived blastema theory) failed to withstand re-examination outside of Lepeshinskaya's group. Zhimkin and Mikhailov concluded that the new theory had been uncritically accepted (it had actually made its way into textbooks of biology, histology and cytology) in an

'unhealthy atmosphere of excessive general adulation'. Her theory was a 'classic example of natural philosophy' in action (i.e. of nineteenth-century German *Naturphilosophie*) (ibid., pp. 183, 185). Interesting in this connexion is the statement by Zhimkin and Mikhailov that Lepeshinskaya's theory was favourably assessed by Alexander Oparin, a recognized authority on the origin of life on this planet. Zhimkin and Mikhailov remarked that there was of course little doubt that 'life arose in the earth in some simple form and cells were formed as a result of a long process of evolution . . . however, it does not follow that the process accomplished formerly, of the development of cells from the primitive living substance is still being effected among the representatives of the animals and plants, and that every cell, in the course of its own development, must pass through the infinitely remote acellular living substance stage' (ibid., p. 185). As for Engels and the cell theory, Zhimkin and Mikhailov say that Engels considered the discovery of the cell and the formulation of the cell theory (presumably Virchow's) to constitute 'one of the most important stages in the development of natural science' (op. cit., p. 182).

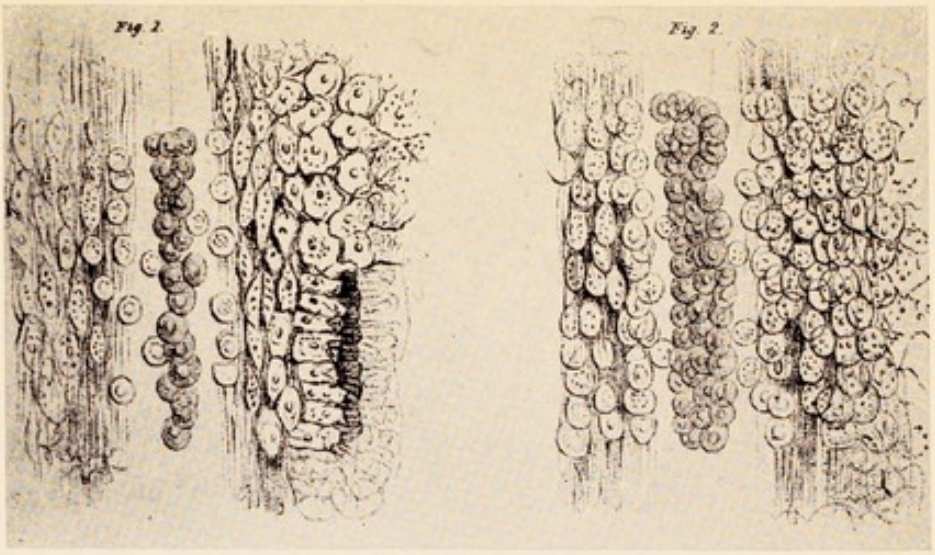

Figure 1. William, Addison, 'The actual process of nutrition in the living structure demonstrated by the microscope . . .', *Trans. Prov. Med. Surg. Assoc.*, 1844, **12** 235–306, Plate II, Figs. 1 and 2. The legends on p. 306 read as follows: (Fig. 1) 'Represents, theoretically, the normal process of nutrition. The colourless blood corpuscles first adhere to the walls of the capillaries; they then contribute to form the walls, and pass through the altering tissue, being evolved upon the nearest free surface in the form of a secretion, epithelial scales, or mucous epithelium.' (Fig. 2) 'Represents, theoretically, an abnormal process of nutrition. The colourless blood corpuscles are in much greater numbers, passing through the altering tissue, and thrown off in the form of pus globules or imperfect epithelial cells.'

Figure 2. William Addison, 'The actual process of nutrition in the living structure demonstrated by the microscope, . . .', *Trans. Prov. Med. Surg. Assoc.*, 1844, **12**, 235–306, Plate I, Fig. 5. The legend on p. 305 reads as follows: 'A blood-vessel in the transparent membrane of a fetal hare; showing altered colourless blood corpuscles, incorporated with the fibres forming the walls of the vessel.'

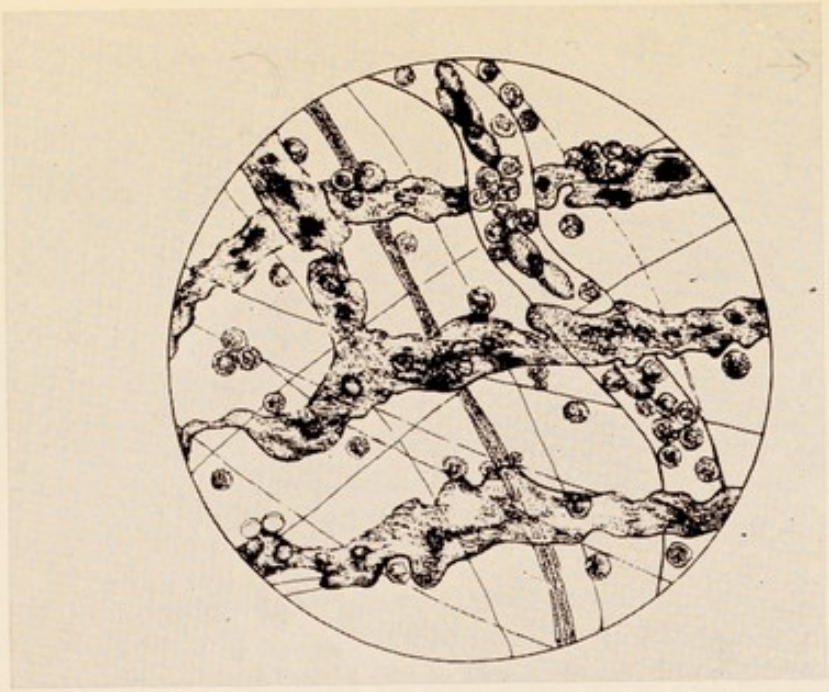

Figure 3. Augustus Waller, 'Microscopic examination of some of the principal tissues of the animal frame, as observed in the tongue of the living frog, toad, etc.', *Phil. Mag.*, 3rd series, 1846, **29**, 397–405, Plate II, Fig. 1 (retouched). The legend on p. 405 reads as follows: 'Represents vessels of the inferior surface of the tongue as they appear after the escape of the corpuscles, filled with stationary blood, deformed and indented at the points of escape, near which the corpuscles are generally found. A portion of a vessel with an internal current is likewise seen with the discs, and internal and external corpuscles. No indentations are seen near these, probably from the force of the current, which directly restored the form of the vessel.' (Slightly retouched.)

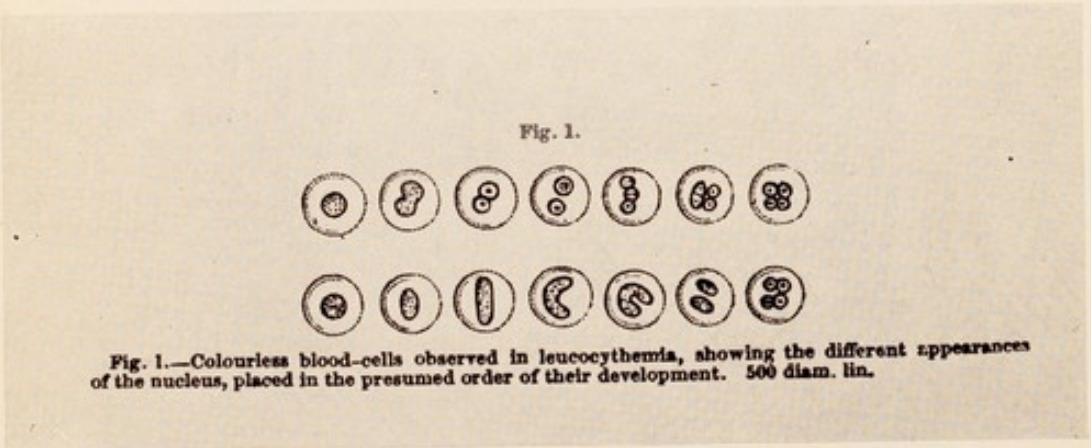

Figure 4. John Hughes Bennett, 'On the function of the spleen and other lymphatic glands', *Mthly J. Med. Sci.*, 1852, **14**, 200–13 Fig. 1, p. 202. The caption reads: 'Colourless blood-cells observed in leucocythemia, showing the different appearances of the nucleus, placed in the presumed order of their development. 500 diam. lin.'

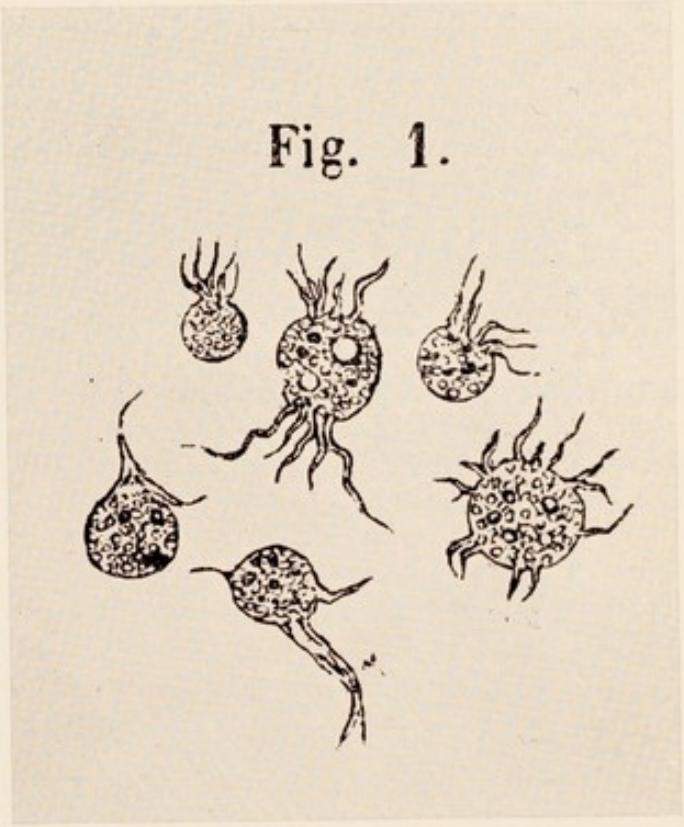

Figure 5. Rudolf Virchow, 'Ueber bewegliche thierische Zellen', *Arch. Path. Anat. Physiol. wiss. Med.*, 1863, **28**, 237–40, Fig. 1, p. 238. The text states that the figure shows the forms taken by mobile cells in fluid from a hydrocele.

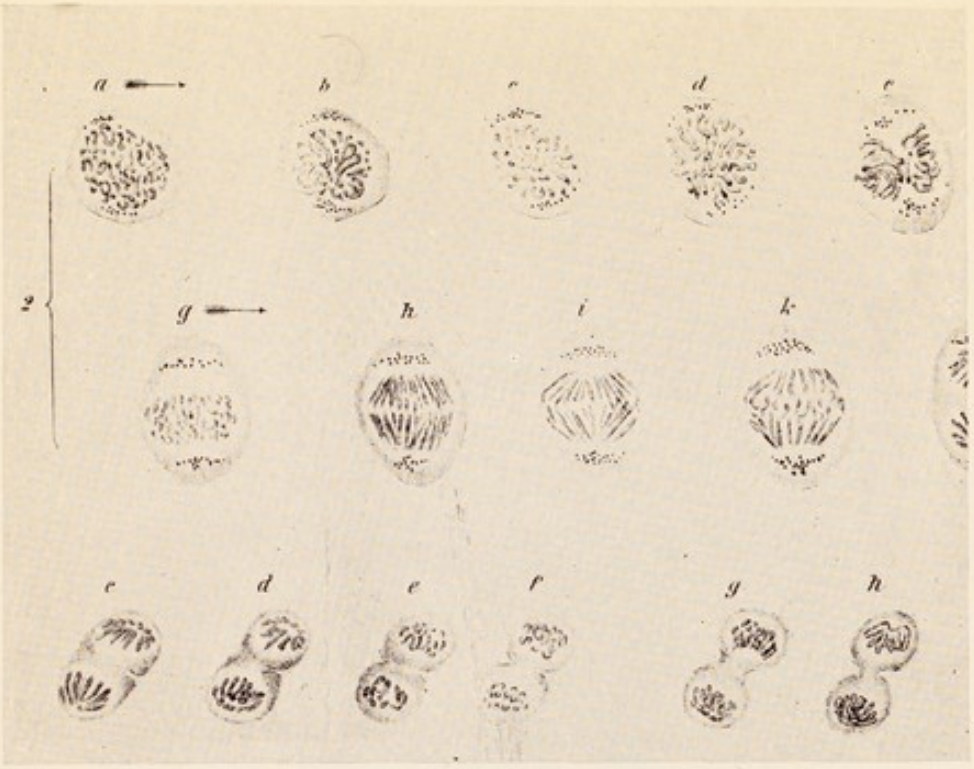

Figure 6. Walther Flemming, 'Beiträge zur Kenntnis der Zelle und ihrer Lebensercheinungen'. *Arch. mikr. Anatomie*, 1879, **16**, 302–436, taf. XVI. 'Successive phases of mitotic division in the dermal epithelium of the larval salamander as seen in living unstained cells.'

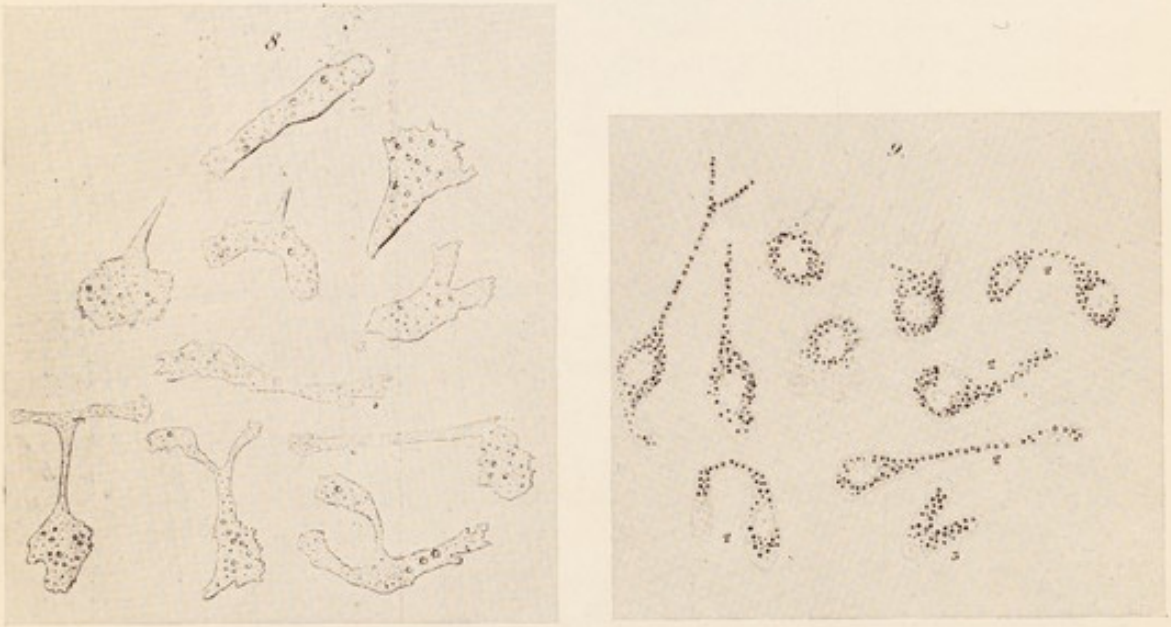

Figure 7. Max Schultze, 'Ein heizbarer Objecttisch und seine Verwendung bei Untersuchungen des Blutes', *Arch. mikr. Anat.*, 1865, **1**, 1–42, Table II, Fig. 8. The legend on p. 42 reads, in translation: 'Finely granulated colourless blood corpuscle on the heated stage at 38°C in active, creeping motion. The forms drawn represent however one and the same corpuscle in its quickly successive changes of shape.' Fig. 9: 'Several coarsely granulated colourless blood corpuscles depicted in the creeping movements taking place at 38°C.'

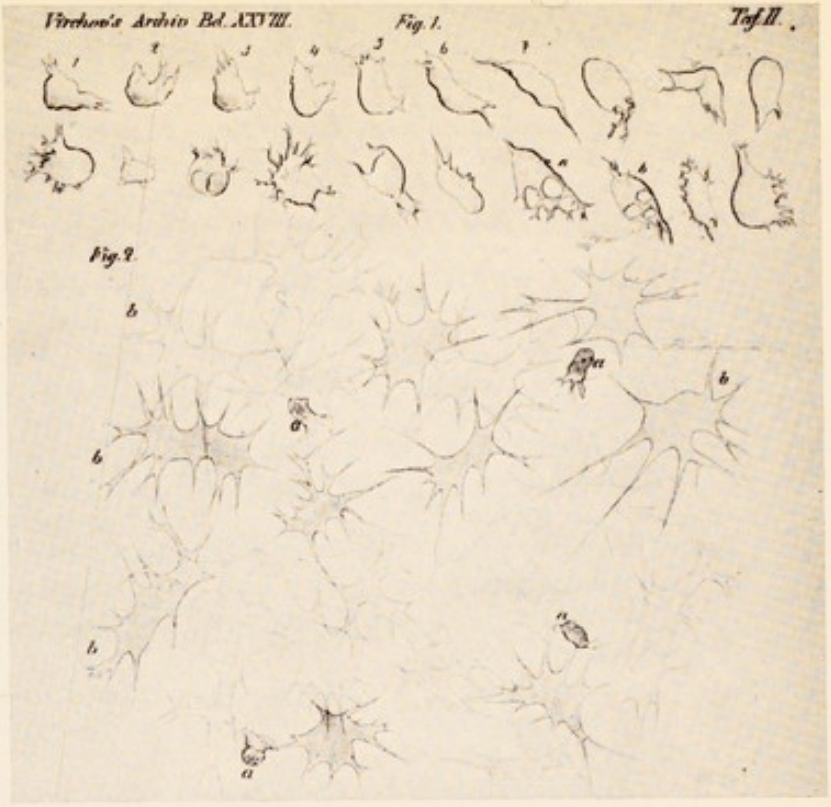

Figure 8. Friedrich von Recklinghausen, 'Ueber Eiter-und Bindegewebskoerperchen', *Arch. path. Anat. Physiol. klin. Med.*, 1863, **28**, 157–97, Table II, Figs. 1–2. The legends on p. 197 read, in translation: (Fig. 1) 'Pus corpuscles of the frog in the aqueous humor; "a" and "b", one and the same corpuscle; 1–7, forms assumed in succession by a corpuscle within five minutes, × 350.' (Fig. 2) 'Cornea of frog, investigated in the moist chamber, "a", four wandering glittering corpuscles; "b", the other branched, immobile, dull corpuscles, × 350.'

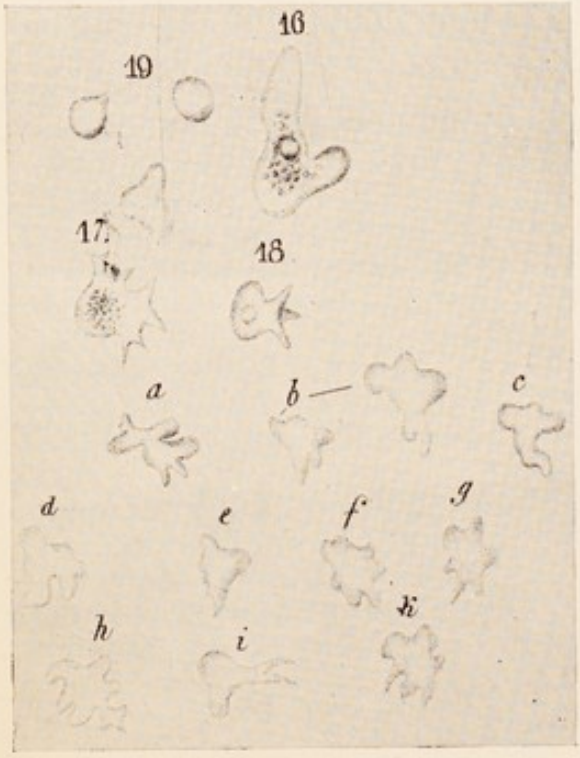

Figure 9. N. Lieberkühn, 'Ueber die Psorospermien', *Arch. Anat. Physiol. wiss. Med.*, 1854, pp. 1–24, Table I, figs. 16–19. The legends on p. 23 read, in translation: (Fig. 16) 'Amoeba from the frog rectum'; (figs. 17–19) 'Colourless blood corpuscles of frogs, specifically in 18 a–k one and the same, the forms shown taking place in succession within ten minutes.'

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a time when it was accepted by almost all major investigators of England and the European continent. The book carries the story of the white blood cells down to the time of Metchnikov. By presenting the various controversies and findings involved, in all their ramifications, over a period covering more than half a century, a hitherto rather veiled aspect of nineteenth-century thought has been brought to light.

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