LEUKAEMIA

Research and Clinical Practice

By

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With 12 coloured plates
and 196 black-and-white illustrations

PREFACE

THE rising incidence of leukaemia and its possible relationship to background or occupational exposure to ionizing radiations in this atomic age have brought the disease increasingly before the public eye. As an example of cellular proliferation, closely akin to the generality of neoplastic processes, leukaemia has been of special interest to innumerable workers in the field of cancer research, since the blood and haemopoietic tissues can be so easily and repeatedly sampled. A multiplicity of techniques, physical, chemical and biological, has been directed to elucidating the nature and fundamental components of the leukaemic state, and in recent times more than a thousand articles about the disease have appeared each year in the world-wide scientific literature.

My intention in writing this book has been to provide a guide through the maze of published work, to separate the tangled lines of progress in research, and to give, in small compass, a reasonably comprehensive survey of current beliefs and activities in both the laboratory and clinical aspects of leukaemia.

Such a diversity of disciplines is applied today to different facets of leukaemia investigation that workers in one discipline do not always find it easy to understand the problems and results of those in another. It is, however, imperative that they should do so, at least in outline, and for this reason I have attempted to provide an appropriate background of elementary principles in each of the research fields discussed, so that the reader unfamiliar with a particular field may nevertheless understand the relevance and intentions of current research within it.

The book contains four chief sections. After a preliminary account of the early history of leukaemia and a short survey of methods used in classifying the disease, the first section is devoted to studies of incidence, ecology and aetiology. Statistical data on the mortality from leukaemia in various countries, on the relative frequency of different forms of the disease, and on the influence of age, sex, race, heredity and environmental factors in man are fully reviewed. Description and discussion of the very important contributions to our knowledge of leukaemogenesis derived from animal experiments and the more restricted experimental work on transmission of leukaemia in man completes the first section. The second section, in which specific studies of the leukaemic cell are described, has separate chapters on cytology and cytochemistry, biochemistry and metabolism, antigenicity and immunology, and *in vitro* cultural characteristics. Emphasis has been given throughout this section to the principles and potentialities of the research methods employed, since these fields of research seem to me the most likely to yield information of decisive and fundamental importance in the understanding and control of leukaemia in the future.

Although the long-term results of treatment of all forms of leukaemia remain highly unsatisfactory at present, dramatic temporary improvement can often be achieved, and the third section of the book is therefore devoted to a discussion of the general principles which appear to govern the modes of action and usages of currently available therapeutic agents, and which may guide the search for more effective new ones. The biological actions of X-rays and radioactive isotopes are considered, and the ways in which chemotherapeutic drugs have been developed and are believed to act are described. Common complications of leukaemia, including anaemia, haemorrhage and infections, are also discussed in this section, with regard both to their pathogenesis and to their treatment.

In the fourth section the clinical aspects of each of the different forms of leukaemia

are dealt with in turn, separate chapters being devoted to the acute leukaemias as a group, to chronic granulocytic leukaemia, to chronic lymphocytic leukaemia, and to unusual varieties of leukaemia. In each case the modes of onset, the extent of system involvements and correlated pathology, the blood and bone marrow changes, the differential diagnosis, the most effective methods of treatment, and the course and prognosis are described and discussed. Illustrative case histories are appended.

In the final chapter the nature and nosology of leukaemia are discussed, with a study of the relationships of the leukaemias to leukaemoid reactions and to other myeloproliferative and lymphoproliferative states.

With regard to nomenclature, the terms defined and described in Chapter 2 have been used throughout the book, but certain synonymous alternatives such as lymphatic and lymphocytic, myeloid and granulocytic, have been used interchangeably; they are so well established in common usage that an insistent preference for one form appears pedantic.

The cytological and cytochemical features of leukaemic cells are illustrated both by colour paintings and by half-tone photomicrographs, a combination designed to achieve a high standard of realism. In the colour paintings and in certain of the photomicrographs a number of identical fields stained by different techniques have been illustrated, thus aiding the comparison of different staining reactions in individual cells. The thirty-six paintings used in the colour plates have been arranged in two ways; they appear first, grouped according to the staining reaction depicted, in the section on cytology and cytochemistry, and a second time, grouped according to the variety of leukaemic cells shown, in the appropriate sections concerned with the different forms of leukaemia. By this means the appearances of blood and bone marrow preparations from all major forms of leukaemia exposed to a single staining procedure can be seen side by side, while later a range of staining reactions in preparations from each individual form of the disease can be compared.

I am grateful to many friends and colleagues who have helped me, directly or indirectly, in the preparation of the manuscript. To my former teacher, the late Sir Lionel Whitby, I owe a special debt, since he encouraged and inspired my interest in leukaemia during the seven years we worked together, and, indeed, first proposed the writing of this book. Among colleagues, past and present, in the University Departments of Medicine, Radiotherapeutics and Pathology and at the Strangeways Institute, are many who have assisted me to clarify ideas by discussion and argument; especially Drs. D. Brinkley, A. Clark, J. H. Crookston, E. Davidson, P. T. Flute, M. Hynes, W. Jacobson, E. M. Kingsley Pillers, D'A. Kok, D. Robertson Smith and H. J. Woodliff, who have worked together with me in the management of many patients with leukaemia, and Dr. A. M. Barrett and his staff, whose scrupulous pathological examinations have been invaluable. The Regius Professor of Physic of Cambridge University, Dr. J. S. Mitchell, kindly read the manuscript, and I am most grateful for his helpful comments and suggestions with reference to the chapter on radiotherapy. I thank also the physicians, surgeons, radiologists and other colleagues in Addenbrooke's Hospital and throughout the East Anglian region who have referred patients to me or helped in their investigation and treatment. Mr. G. F. Wright, ophthalmologist to the United Cambridge Hospitals, kindly took several retinal photographs for my use and I am most grateful to him for his help. With Drs. D. Gairdner and J. Roscoe, paediatricians to the United Cambridge Hospitals, I have had many helpful discussions during our joint control of children with acute

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CONTENTS

CHAPTER 1

HISTORY OF LEUKAEMIA

TOWARDS the middle of the nineteenth century the time became ripe for the recognition of leukaemia. Cases of splenic enlargement accompanied by pallor, purpura, lymphatic glandular swelling and other signs commonly found in leukaemias had been described often since the earliest medical records. A paper entitled "Observations on abdominal tumours and intumescence: illustrated by cases of diseases of the spleen, with remarks on the general pathology of that viscus", from the pen of the eminent Richard Bright of Guy's Hospital, Physician Extraordinary to the Queen, makes clear the position of advanced medical opinion on this subject in 1838. "With regard to the functions of the spleen", he wrote, "we have every reason to believe that it affords important assistance in preparing the blood; but whether chiefly as accessory to the process of digestion, or as having within itself the power of acting beneficially on the blood, I shall not now consider it necessary to inquire: it is an established fact, that it is provided with a structure which affords it peculiar elasticity so that it can accommodate itself to great changes in the volume of the blood it contains." Among a large number of "structural alterations" of the spleen categorized by Bright and including congestion, hardening, softening, inflammation, suppuration, gangrene, tuberculosis, malignant disease, melanosis and a form of splenic disease "particularly pointed out by Dr. Hodgkin as connected with extensive disease of the absorbent glands" is to be found a condition described as "fleshy hardness with enlargement". Bright noted that "In this state, the spleen often attains to a prodigious size, filling up the whole left side of the abdomen. It produces very little constitutional irritation, and chiefly injures by its bulk, and its tendency to favour serous effusion. It is astonishing with what rapidity this enormous growth occasionally takes place; but in this respect we are liable to be deceived, for it is attended by so little pain, that, in many cases, the increase has been taking place, gradually, long before some accidental circumstance leads to its discovery. In young children, this form of disease is still more frequent than in adults; and with them it is more fatal. It often begins to shew itself at two or three months of age, gradually increasing, till it bears a very large proportion to the whole contents of the abdomen; and it is to be traced quite into the pelvis, and extending far beyond the linea alba, towards the right side. In these cases, it is often attended with the appearance of petechiae all over their cadaverous and pale bodies. Such children seldom live above a year, or two or three; and fall victims to emaciation and often to mesenteric disease." Although Bright included many case reports in this instructive article and one may reasonably interpret several of them as examples of some form of leukaemia, no reference appears to blood examination, either macroscopic or microscopic, during life or *post mortem*. Yet how near Bright and, no doubt, many of his contemporaries were to the concept of splenic involvement in a generalized blood disease may be seen from his

penetrating final remarks in this paper. "I may observe generally in reference to splenic disease," he wrote, "that it is probable that the spleen is greatly influenced by the derangement of many of the other organs of the body: . . . for we cannot doubt, that whatever acts decidedly on the circulating system, must, in some degree, influence the spleen; which obviously, from its structure and appearance, receives large quantities of blood, as subsidiary to the processes of sanguification or circulation."

While clinicians were so close to the idea of a disorder of "sanguification" involving the spleen, pathologists and microscopists had been surprisingly slow to exploit and extend the microscopic studies of blood and the recognition of "white globules" initiated by William Hewson in 1774. According to Gowers (1879), "examples of a peculiar alteration in the colour of the blood, suggesting the admixture with it of pus", had been recorded by Bichat and others in the early years of the nineteenth century, and Velpeau in 1827 described a patient with enlargement of the spleen and a rather similar naked-eye appearance of the blood, like the lees of wine, but no microscopic study was carried out and these macroscopic changes cannot be attributed definitely to increased leucocyte content. The same is true of certain earlier records of a milky appearance of blood, such as that of von Haller, quoted by Virchow in 1845.

The clear recognition of leukaemia awaited the marriage of clinical and microscopic evidence, and this was brought about independently in several centres within a span of half a dozen years, between 1839 and 1845. Priority is not easy to allocate, since observation in some cases preceded publication by a number of years, while some early observers did not appreciate the significance of their discovery. A somewhat heated controversy on this question of priority mars the early pages of leukaemia's history (see Gowers, 1879; Osler, 1885; Rolleston, 1934; Dreyfus, 1949), but we need not today be unduly concerned with the allocation of credit. The discovery was not in any case a stroke of genius; the extensive application of morbid anatomical and microscopic methods to clinical problems had made it inevitable.

In France the disease was probably first recognized by Barth and Donné. A woman of 44 years with gross splenic enlargement was admitted to the Hotel Dieu in Paris in 1839, under the care of Barth. At post-mortem examination the blood was found to be semi-purulent, and microscopic study carried out by Donné showed that more than half the blood cells were "white globules". Although this patient was studied in 1839, Barth did not report his observations publicly until 1855 and the records were not published until 1856. Donné had, however, made reference to his microscopic findings in a monograph, "Cours de microscopie complémentaire des études médicales, anatomie microscopique et physiologie des fluides de l'économie", which appeared in 1844. Here he noted (p. 197): "J'ai plusieurs fois rencontré dans le sang de malades, des proportions considérable de globules ayant tous les caractères des globules de pus, et que j'aurais infailliblement considérés comme tels, si je n'avais pas connu d'une part, la grande analogie de structure et de forme des globules purulents avec les globules blancs du sang, et de l'autre si la nature de la maladie et l'autopsie n'avaient pas éloigné toute idée de pus circulant avec le sang." We may reasonably assume that Barth's case was among the "several" here mentioned, and may perhaps also conclude that Donné had studied the blood of other leukaemic patients, since he is more likely to have noted the very high leucocyte numbers in leukaemia than the moderately increased numbers in inflammatory leucocytoses, and, more-

over, both the clinical and autopsy findings in the cases referred to in the quotation above seem to have made pyogenic infection an unlikely diagnosis. Elsewhere (p. 135) in Donné's treatise, indeed, there appears a case report of a further patient, undoubtedly suffering from leukaemia, whom he had seen during life at the Hôpital de la Charité. "Un homme, dans la force de l'âge, était atteint d'une artérite qui affectait spécialement les vaisseaux des membres inférieurs; les deux jambes étaient le siége d'ecchymoses, de phlyctènes gangreneuses, etc. Le sang de ce malade présentait une telle quantité de globules blancs, qu'en raison même de la nature de son affection j'étais porté à croire que le sang était réellement mêlé de pus; mais, en définitive, il ne me fut pas possible de constater une difference tranchée entre ces globules et les globules blancs."

In 1845, the year following the publication of Donné's monograph, cases of leukaemia with clinical, post-mortem and microscopic findings were independently and almost simultaneously published in Edinburgh and Berlin. In the *Edinburgh Medical and Surgical Journal* of October 1, 1845, two case reports appeared under the title "Disease and Enlargement of the Spleen in which Death took place from the Presence of purulent matter in the Blood". In the first, David Craigie described a patient who had been under his care in 1841; autopsy, performed by John Reid, revealed "globules of purulent matter" in the blood, great enlargement of the spleen, which weighed 115½ oz. and enlargement of the liver to 99 oz. Mesenteric glands were also noted to be enlarged and the kidneys contained scattered white spots.

It seems likely that neither Craigie nor Reid appreciated the significance of these findings, and the case might not have been recalled or put on record had not Craigie been present at the post-mortem examination of a second, very similar case. An account of this second case immediately follows that of Craigie in the *Edinburgh Journal* of October 1845. The patient had been under the care of Sir Robert Christison, but was described by John Hughes Bennett, who himself performed the autopsy and examined the blood microscopically. The patient, a man of 28 years, had complained of increasing lassitude for 20 months and a growing tumour in the left side of the abdomen for 7 months. The abdominal mass, painless at first, had become painful during the few weeks preceding his admission to hospital and tender enlarged glands had appeared in the neck, axillae and groins. In hospital he was feverish with a rapid full pulse, developed diarrhoea and died suddenly about 21 months after the first appearance of symptoms.

When Bennett carried out the post-mortem examination, 4 days after death, he noted that parts of the blood clot were uncommonly yellow, opaque and dull in appearance and that material resembling thick pus could be squeezed from the cut ends of many veins. The walls of the vessels and heart did not appear diseased. There was great enlargement of the spleen, which weighed 124 oz. and had a firm yellow "exudation", an inch deep and three inches long, on its anterior surface. The liver was also enormously enlarged, weighing 172 oz. Bennett described these enlargements as "simple hypertrophy". Diseased lymphatic glands, some almost as big as a hen's egg, were found in the inguinal and axillary regions. Glands in the bronchial, mesenteric and lumbar groups were also enlarged and showed on section a greenish-yellow cut surface.

Microscopic study of the blood clot showed the presence of large numbers of colourless corpuscles between an eightieth and a hundred and twentieth of a millimetre in diameter. Bennett, who perhaps first became familiar with the microscopic appearances of blood

when he earlier attended lectures given in Paris by Donné, fully described his findings in blood, spleen and glands.

The colourless corpuscles of the blood clot "were round, their cell wall granular, and they presented all the appearance of pus corpuscles. Water caused them to swell and lose their granular appearance, and acetic acid dissolved the cell wall and caused a distinct nucleus to appear. The nucleus was composed sometimes of one large granule about one two-hundredth of a millimetre in diameter, at others of two or three smaller granules, as is seen in the corpuscles of laudable purulent matter.

"The exudation in the spleen was composed of amorphous fibrin mixed with numerous molecules, granular and imperfect cells. These were intermingled with bundles of filamentous tissue. The enlarged lumbar glands, on being pressed, exuded a fluid that was crowded with corpuscles; some resembling the colourless corpuscles already alluded to; others oval and round, containing a distinct nucleus."

Neither Craigie nor Bennett regarded the diseases they described as primary disturbances of leucopoiesis. Craigie thought the disorder to be due to chronic inflammation of the spleen and argued that the structure of the spleen was such that pus formed there would not accumulate as an abscess but pass directly into the blood stream. Bennett also thought the colourless corpuscles were pus cells rather than white blood cells and concluded that the disease was a suppuration of the blood.

It was left for Virchow in his description of a further similar case, published in November 1845, to recognize the peculiar and individual nature of the disease, to identify the abnormal corpuscles in the blood as white blood cells, and later, in 1847, to propose a new name, "leukaemia", for the disorder. This name did not receive unqualified acceptance, for in a paper read to the Société de Biologie in Paris in April 1851, Bennett, after describing and discussing four cases studied personally and a further eight culled from the literature, objected to the term "leukaemia" as a misnomer, since the blood in this disease was not itself white. He proposed "leucocythemia" (λεκὸς, white, κύτος, cell, and αἷμα blood) as a more satisfactory descriptive term. He did, however, accept Virchow's interpretation of the nature of the disease and withdraw his former concept of blood suppuration. We must agree with Gowers, who discussed this problem of terminology in 1879, that "Leucocythemia" would really be a more apt and accurate name, particularly since the white blood corpuscles came to be generally known as "leucocytes" after the first appearance of this word in 1855 in M. P. Littré and C. Robin's Dictionnaire de Médecine (Nysten), but, perhaps because it is shorter, "leukaemia" seems now firmly established.

The cases of leukaemia described by Barth and Donné, Craigie, Bennett and Virchow were all ones in which the blood condition was recognized only *post mortem*. In December 1845 a patient was admitted to St. George's Hospital, London, under the care of Dr. Nairne, with a history of langour and depression for 8 months and a rapidly increasing left hypochondriac tumour. After his death in January 1846, gross splenomegaly and hepatomegaly were found at autopsy and the blood was noted macroscopically to be of a peculiarly grey colour. Henry Fuller, who reported this case to the Royal Medical and Chirurgical Society in June 1846, stated that he had three times during life examined this patient's blood microscopically and again after death, and on each occasion he found, in addition to the natural blood corpuscles, a very large proportion of abnormal, granular,

colourless globules. He was inclined to believe that this disease was induced by exposure to malaria and consisted of a perversion of the nutritive functions, but he argued that "instead of viewing the enlargement of the spleen as the principal object for investigation, it will be consistent with a correct view of the disease to speak of the enlargement of the spleen as one of the phenomena usually attendant on a peculiar form of constitutional disorder." This is probably the first account of a case recognized in life, but during the next few years diagnosis of leukaemia in the hospital wards became commonplace, as examination of blood under the microscope came to be more often employed in suspected cases of the disease. Gowers (1879) recalled that, in August 1846, W. H. Walshe demonstrated to students in his class at University College Hospital, London, that "colourless corpuscles were as numerous as the coloured discs" in the blood of a patient with enlargement of the spleen. Vogel, in 1849, was apparently the first to make similar observations during life, in Germany, but other records rapidly began to appear in print after this time and an expanding and voluminous literature on leukaemia began to accumulate. John Hughes Bennett published a treatise on leucocythemia in 1852 in which he included a number of new cases and gave further details of the morbid histology, while Virchow, after republishing some collected cases, with additional comment, in 1846 and 1847, continued to make valuable contributions to the study of leukaemic pathology and physiology over the ensuing years (1849, 1853, 1864, etc.). Among the many papers, now far too numerous to list, which appeared during these years we may particularly note Biermer's first record of leukaemia in childhood (1861) and Bryant's early unsuccessful attempt to halt the progress of the disease by removing the spleen (1866).

Meanwhile, the conversion of general physicians to the idea of this newly defined disease was gradually occurring, a process well exemplified in the remarks appended by Dr. Samuel Wilks of Guy's Hospital to his report of two further cases diagnosed during life, published in 1855. He wrote: "The above cases assist in confirming the observations made by Dr. Hughes Bennett respecting the connection of enlargement of the spleen with an excess of white globules in the blood; and they are of the more value because they contrast with a large number of other cases (having no disease of this viscus) where a trial of the blood was made and no leucemic condition found. For with the first scepticism which attends the reading of all novel discoveries, there arose the idea of testing the blood in various other cases, where a diseased state of this fluid might reasonably be suspected, in order to ascertain whether only one organ was capable of producing it. The best for this purpose were thought to be all cases of suspicious abdominal tumours, whose constitution was uncertain, as well as the simple enlargements of the spleen in ague, and other cases where a dyscrasic state of the blood was well-marked, as in scurvy, and purpura. I have examined the blood in a large number of instances of these various diseases, and have notes of about fifty, and in none, except the two described above, did its condition approach to what could be called leucocythaemia. In . . . that class of cases which has especially gained the attention of Dr. Addison, and which he has designated idiopathic anaemia, and where, above all others, it might be presumed that the existence of an excess of colourless globules was probable, no such condition has, as a rule, been found. In purpura and scurvy, also, there is no perceptible deviation from the normal relation of the two kinds of corpuscles."

Although in these early years leukaemia was chiefly discovered in association with gross

splenomegaly, Virchow, in 1847, differentiated two forms of the disease, splenic and lymphatic, and emphasized the importance of lymph node involvement particularly in the latter form. Further major advance had to await the discovery of specific staining methods for blood cells and the rise of haematological cytology, and contributions to the study of leukaemia in the interim tended to be of uncertain interpretation and were often frankly confusing. Thus Cohnheim, in 1865, used the term "pseudoleukaemia" to describe a case with lymphatic glands showing the histological picture of leukaemia but with no significant changes in the peripheral blood. This condition may have been aleukaemic leukaemia, but, since the study of lymph gland pathological histology was still in its infancy, it may equally well have been Hodgkin's disease or some other predominantly lymphomatous disease. Again, Neumann's reports of extensive changes in the bone marrow in leukaemia (1870, 1872, 1878), while of fundamental importance, led to difficulties in classification and nomenclature, since he now separated a third category of leukaemia, myelogenous, from the recognized splenic and lymphatic forms.

The introduction of differential staining methods, developed and expanded by Paul Ehrlich from 1877 onwards and described in his monograph "Farbenanalytische Untersuchungen zur Histologie und Klinik des Blutes" (1891), greatly facilitated fresh advance of knowledge about leukaemia as in so many haematological fields. As early as 1879, Ehrlich had published his findings on the specific granules of leucocytes and classified them as eosinophil, neutrophil and basophil. He distinguished all the varieties of normal peripheral blood white cells that we now recognize and made numerous and mainly accurate observations on the blood in leukaemias. Qualitative study of the blood films from cases of leukaemia, with differentiation of the various types of cell present, now came to replace the former rough assessments, and it was soon apparent that Virchow's "splenic" leukaemia was essentially identical with the "myelogenous" leukaemia of Neumann. At this stage two major subdivisions of leukaemia were thought to exist, the "splenomyelogenous" form in which large numbers of polymorphonuclear and mononuclear cells containing specific granules were present in the blood, and the lymphatic form in which many non-granular, mononuclear lymphocytic cells were found.

An increasing number of cases next came to attention in which the cells of the peripheral blood included differing proportions of both granulocytes and large atypical non-granular, mononuclear cells, and these were at first regarded as mixed leukaemias. What we now know to be the acute myeloblastic termination of myelogenous leukaemia was also observed and taken to be a transformation from myelogenous to lymphatic leukaemia. The confusion thus brought about began to be clarified when Otto Naegeli, in 1900, recognized and described the myeloblast. The existence of such a non-granular, mononuclear precursor of the granulocyte series of cells provided an explanation for the "mixed" leukaemias and the transformation anomalies, and the idea of different phases of leukaemia with varying proportions of mature and immature cells was established. The acceptance of the myeloblast as an immature cell of both normal and pathological marrow, with potentialities for development along the granulocyte line—quite different from the lymphocyte with which it had previously been confused—was assisted by the introduction of oxidase and peroxidase staining techniques. These methods, modified and applied to blood and bone marrow cells by Graham (1916), Goodpasture (1918) and later many others, confirmed Naegeli's views on the place of the myeloblast by enabling intermediate stages

between the most primitive myeloblast and the fully granular myelocyte to be clearly demonstrated.

The recognition of the myeloblast contributed also to the understanding of acute leukaemic states. In 1857 Friedrich had noted the occurrence of a new form of leukaemia with a rapid, acute course, and Gowers (1879) made reference in his review of "splenic leucocythaemia" to "many cases on record in which the symptoms lasted six months only" and some with an even shorter course. He stated, however, that "the most acute cases on record, in which the disease runs its course in a few weeks, are usually attended with great and rapid enlargement of the lymphatic glands and spleen", and since this picture is hardly typical of acute leukaemia as we now know it, the cases may have been examples of acute terminal exacerbation of previously undetected chronic granulocytic leukaemia. The distinction of acute from chronic leukaemia came about gradually; Ebstein, in 1889, described the clinical picture of acute leukaemia on the basis of 16 cases already recorded in the literature, and Fraenkel, in 1895, made a careful study of the blood cells in this condition. Fraenkel assumed that the atypical mononuclear cells he found were early lymphocytes, and he and most of his contemporaries believed that all acute leukaemias were lymphocytic, but he nevertheless concluded that these "lymphocytes" were young forms capable of transforming into polynuclear cells. Ehrlich, writing on "Histology of the blood, normal and pathologic" in Nothnagel's Encyclopaedia of Practical Medicine (English edition, 1905), treats these views of Fraenkel with the greatest contempt. Fraenkel attributed the decrease of polynuclear cells in acute leukaemia to "a disturbance of the conditions necessary for transformation of young forms", that is, to a defect of maturation, and made the difference between acute and chronic leukaemia to be "that in the former the newly formed elements are thrown off from their place of origin into the circulation with such extraordinary rapidity that time is wanting for complete development, while in chronic leukaemia the transition is probably much slower". Ehrlich, who at the time he wrote his article for Nothnagel clearly believed all non-granular mononuclear cells of the blood to be either monocytes or lymphocytes and incapable of becoming anything else, regarded Fraenkel's views as "plainly contradictory to the facts" and found it "very difficult to conceive of conditions which would prevent the natural maturing" of the blood elements. The identification of the myeloblast and the appreciation of its potentialities went far to reconcile the conflicting views; acute leukaemias might be either "lymphogenous" or "myelogenous", and while the majority of peripheral blood leucocytes in either case were non-granular, in the one case their development was restricted to the non-granular lymphocyte line while in the other a tendency, more or less marked, might be shown to develop along the myelocytic chain.

Leukaemias recognized before 1913 were all regarded as examples of disease of the lymphocytic or granulocytic series of cells, and the occurrence of a leukaemic proliferation of monocytes had not been reported, but in that year Reschad and Schilling-Torgau (1913) described a new form of leukaemia involving "splenocytes" or monocytes. The cytological study made by these authors does not appear to have convinced many haematologists of the existence of monocytic leukaemia as a separate entity, for in the next 15 years only six further cases were reported (Clough, 1932), but from about 1930 onwards increasing numbers of reports evidenced the spreading acceptance of the concept.

With the definition of a monocytic variety of the disease, the major landmarks in the

panorama of leukaemia had been identified. Controversy over borderline states, interrelationships and innumerable details continued, and indeed is still maintained today, but a general concept of leukaemia had emerged that has not required radical modification in the last 30 years.

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CHAPTER 2

GENERAL CONCEPT AND CLASSIFICATION

THE name leukaemia refers not to a single clear-cut entity, but to a group of disorders in which proliferation, maturation and release of leucocytes and related cells are no longer kept within bounds by the normal physiological mechanisms of control. There is enormously increased activity at sites of leucopoiesis and these sites greatly expand, while large numbers of leucocytes, including immature forms, are often released into the circulation and are found infiltrating many tissues. The disease, untreated, is invariably fatal, and no successful form of curative or permanently controlling therapy has yet been discovered.

Classification

In classifying leukaemias reference may be made to the clinical acuteness of the disease, the number of leucocytes circulating in the peripheral blood and the presence of abnormal forms, the identity of the predominating cells and their stage of maturity, and the site of origin of the proliferating leucocytes. In addition, the need for clarity and consistency in nomenclature must be met as far as possible, and this is not altogether easy when cells of wide potentialities and uncertain relationships are involved. Finally, certain "paraleukaemic" states must be discussed.

Acuteness of the disease

A general distinction can be made on clinical grounds between acute and chronic leukaemias. In the former the onset is commonly rapid and the course short and severe, with dramatic symptoms and physical signs of fever, anaemia, haemorrhage, tissue infiltrations, buccal ulceration, secondary infections of respiratory tract, and the like; if the disease is untreated, death usually occurs within 3 months of the onset. In chronic leukaemia, on the other hand, the date of onset is often uncertain, so insidiously do symptoms commence; the condition progresses relatively slowly and may remain mild for long periods with few manifestations of disease other than painless splenomegaly or lymphatic glandular enlargement. Patients with chronic leukaemias nearly always survive more than a year from the time of first symptoms, commonly for 3 to 5 years, and occasionally for very much longer. The survival differences between acute and chronic forms of the disease have been used to provide arbitrary limits, cases of duration less than 3 months (Sturgis, 1955) or 6 months (Custer, 1949) being regarded as acute, those of more than a year's duration being called chronic, while cases of intermediate survival, between 3 or 6 months and 1 year, are described as subacute. Such criteria may be validly applied to many cases of untreated leukaemia, but their general rigid adoption would be quite unsatisfactory for a variety of reasons. Cases with the classical presentation of acute leukaemia, when treated by methods now available, often survive for longer than 6 months and, indeed,