HISTOLOGICAL AND CYTOLOGICAL TYPING OF NEOPLASTIC DISEASES OF HAEMATOPOIETIC AND LYMPHOID TISSUES

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No. 1. Histological typing of lung tumours, by Leiv Kreyberg in collaboration with A. A. Liebow and E. A. Uehlinger (1967)


No. 3. Histological typing of soft tissue tumours, by F. M. Enzinger in collaboration with R. Lattes and H. Torloni (1969)


No. 6. Histological typing of bone tumours, by F. Schajowicz, L. V. Ackerman, and H. A. Sissons in collaboration with L. H. Sobin and H. Torloni (1972)

No. 7. Histological typing of salivary gland tumours, by A. C. Thackray in collaboration with L. H. Sobin (1972)


No. 9. Histological typing of ovarian tumours, by S. F. Serov and R. E. Scully in collaboration with L. H. Sobin (1973)


No. 11. Histological typing of thyroid tumours, by Chr. Hedinger in collaboration with L. H. Sobin (1974)


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GENERAL PREFACE TO THE SERIES

Among the prerequisites for comparative studies of cancer are international agreement on histological criteria for the classification of cancer types and a standardized nomenclature. At present, pathologists use different terms for the same pathological entity, and furthermore the same term is sometimes applied to lesions of different types. An internationally agreed classification of tumours, acceptable alike to physicians, surgeons, radiologists, pathologists and statisticians, would enable cancer workers in all parts of the world to compare their findings and would facilitate collaboration among them.

In a report published in 1952, a subcommittee of the WHO Expert Committee on Health Statistics discussed the general principles that should govern the statistical classification of tumours and agreed that, to ensure the necessary flexibility and ease in coding, three separate classifications were needed according to (1) anatomical site, (2) histological type, and (3) degree of malignancy. A classification according to anatomical site is available in the International Classification of Diseases.\(^1\)

The question of establishing a universally accepted classification by histological type has received much attention during the last 20 years and a particularly valuable Atlas of Tumor Pathology—already numbering more than 40 volumes—is being published in the USA by the Armed Forces Institute of Pathology under the auspices of the National Research Council. An Illustrated Tumour Nomenclature in English, French, German, Latin, Russian, and Spanish has also been published by the International Union Against Cancer (UICC).

In 1956 the WHO Executive Board passed a resolution\(^3\) requesting the Director-General to explore the possibility that WHO might organize centres in various parts of the world and arrange for the collection of human tissues and their histological classification. The main purpose of such centres would be to develop histological definitions of cancer types and to facilitate the wide adoption of a uniform nomenclature. This resolution was endorsed by the Tenth World Health Assembly in May 1957\(^4\) and the following month a Study Group on Histological Classification of Cancer Types met in Oslo to

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advise WHO on its implementation. The Group recommended criteria for selecting tumour sites for study and suggested a procedure for the drafting of histological classifications and testing their validity. Briefly, the procedure is as follows:

For each tumour site, a tentative histopathological typing and classification is drawn up by a group of experts, consisting of up to ten pathologists working in the field in question. An international reference centre and a number of collaborating laboratories are then designated by WHO to evaluate the proposed classification. These laboratories exchange histological preparations, accompanied by clinical information. The histological typing is then made in accordance with the proposed classification. Subsequently, one or more technical meetings are called by WHO to facilitate an exchange of opinions and the classification is amended to take account of criticisms.

In addition to preparing the publication and the photomicrographs for it, the reference centre produces up to 100 sets of microscope slides showing the major histological types for distribution to national societies of pathology.

Since 1958, WHO has established 23 centres covering tumours of the lung; breast; soft tissues; oropharynx; bone; ovaries; salivary glands; thyroid; skin; male urogenital tract; jaws; female genital tract; stomach and oesophagus; intestines; central nervous system; liver, biliary tract and pancreas; upper respiratory tract; eye; and endocrine glands; as well as oral precancerous conditions; the leukaemias and lymphomas; comparative oncology; and exfoliative cytology. This work has involved more than 300 pathologists from over 50 countries. A number of these centres have completed their work, and most of their classifications have already been published (see page 6).

The World Health Organization is indebted to the many pathologists who have participated and are participating in this large undertaking. The pioneer work of many other international and national organizations in the field of histological classification of tumours has greatly facilitated the task undertaken by WHO. Particular gratitude is expressed to the National Cancer Institute, USA, which, through the National Research Council and the USA National Committee for the International Council of Societies of Pathology, is providing financial support to accelerate this work. Finally, WHO wishes to record its appreciation of the valuable help it has received from the International Council of Societies of Pathology (ICSP) in proposing participants and in undertaking to distribute copies of the classifications, with corresponding sets of microscope slides, to national societies of pathology all over the world.
PREFACE TO
HISTOLOGICAL AND CYTOLOGICAL TYPING OF
NEOPLASTIC DISEASES OF
HAEMATOPOIETIC AND LYMPHOID TISSUES

The WHO International Reference Centre for the Histological and Cytological Classification of Neoplastic Diseases of the Haematopoietic and Lymphoid Tissues was established in 1962 at the Institut de Cancérologie et d’Immunogénétique, Groupe hospitalier Paul-Brousse, Villejuif, France. At a meeting in Geneva in 1961, a tentative classification of these diseases was drafted. This was then evaluated by the International Reference Centre and the participants (see page 5).

The International Reference Centre distributed to the participants material (smears, imprints, and histological sections) from selected cases of neoplastic diseases of haematopoietic and lymphoid tissues for typing according to the tentative classification. In all, 200 cases were studied and reviewed at meetings held in 1966 and 1968.

The authors then prepared the accompanying text and colour photomicrographs. The latter are reproduced as colour plates in this book and are also available as a collection of transparencies intended especially for teaching purposes. To help pathologists who may wish to know the corresponding terms in French, Russian, and Spanish, translations of the classification into these languages are also given, immediately following the English version.

Classification of haematopoietic and lymphoid neoplastic diseases is currently in an unstable state owing to fast-moving developments in this field. New histogenetic and immunological concepts are being formulated at a rapid rate. Even during the course of the preparation of this publication a number of new nosological approaches have been put forward. The results of several international workshops and meetings have therefore played a role in the formulation of this classification. Consideration of these new developments has, in fact, delayed publication. Although there is still lack of agreement in several areas, it is felt that publication at this stage will have the benefit of providing a degree of stability in the recording of comparable data while conceptual work continues in this field. Although it represents a view from which some may wish to dissent, it is nevertheless hoped that, in the interests of international cooperation, all pathologists and haematologists will try to use the classification as it now stands until a more definitive, unified classification is formulated and
accepted. Criticisms and suggestions for its improvement will be welcomed; they should be sent to the World Health Organization, Geneva, Switzerland.

The publications in the series International Histological Classification of Tumours are not intended to serve as textbooks but rather to promote the adoption of a uniform terminology of tumours that will facilitate and improve communication among cancer workers. For this reason, the literature references have been intentionally kept to a minimum and readers are referred to standard works on the subject for extensive bibliographies.
INTRODUCTION

The classification of neoplastic diseases of the haematopoietic and lymphoid tissues is based primarily on the predominating component cell type. Moreover, the main clinical and gross morphological patterns are taken into account; tumours that are initially localized or circumscribed are separated from diseases that appear to be systemic from their clinical onset. This in no way implies that a sharp differentiation between the two forms of involvement can always be made. For example, circumscribed and diffuse infiltrations may occur simultaneously or consecutively in one patient, and in some instances a tumour initially localized to an area not readily accessible to clinical observation, such as retroperitoneal lymph nodes, may escape detection until the disease has assumed the proportions of a systemic disorder.

It must also be emphasized that the arrangement chosen for tabulation of this classification scheme does not imply that the precise nature of the tumour cells is well established in all the conditions listed. While there is no doubt, for instance, that the myeloma cell is a neoplastic plasma cell, there is no proof that the proliferating “lymphoblastic” cell of acute lymphoid leukaemia is, in fact, the precursor cell of the lymphocyte.

The morphological difference between the plasma cells seen in myeloma and the cells of similar appearance that are intermingled with the lymphocytes in primary macroglobulinaemia (Waldenström) may be slight or nonexistent, yet the two diseases are usually readily distinguishable clinically and immunochromically.

The non-neoplastic counterpart of the predominant cell in Burkitt’s tumour has not been clearly established, but the character of the nuclear chromatin, the prominence of the nucleoli in well-prepared smears or imprints, and the intense basophilia (pyroninophilia) of the cytoplasm, which may contain vacuoles, make this cell resemble lymphocytes “transformed” by mitogens or by antigenic stimulation—cells that, at least in the latter case, are usually called “immunoblasts”.¹

Moreover, some authors differentiate “immunoblastic” acute lymphoid leukaemia and “immunoblastic” lymphosarcoma from Burkitt’s tumour.

¹ In accordance with present knowledge, histopathologists and haematologists apply the term immunoblast to large lymphoid cells with pyroninophilic or Giemsa-positive, very basophilic cytoplasm. However, these tinctorial properties do not constitute absolute proof that these cells are immunoblasts; they merely indicate a high cytoplasmic RNA content.
The distinction lies not only in the histological features but also in the immunological properties (markers) of the cells: while those of Burkitt's tumour are B (bone-marrow-derived) lymphoid elements, those of "immuno­blastic" lymphoid leukaemia and lymphosarcoma may be B or T (thymus-dependent) lymphoid elements.

In the context of this classification, the term "lymphoid" is used to designate the leukaemias of the lymphocytic or presumably lymphocytic lines. Though this term is less precise than "lymphoblastic" and "lymphocytic", it is being used intentionally because new knowledge in lymphocyte physiology is becoming available that may lead to the recognition of new entities. By using a less specific term, integration of such new entities into the proposed classification may be facilitated.

For example, much work has recently been carried out on the classification of lymphoid neoplasias according to T or B immunological markers carried by the cells. Though it has been claimed that some T lymphoid neoplasias can be recognized on the basis of the convoluted nuclei of their cells, and some B neoplasias on the basis of the cleaved nuclei of the tumour cells, histopathologists and cytologists are recommended to limit themselves to mentioning such observations and not to draw conclusions from these characteristics as to the T-cell or B-cell nature of the lymphoid tumours, which can be determined only by immunological investigation.

In recognition of its wide usage and general acceptance, the historical term "reticulosarcoma" has been retained only for those tumours considered to be composed of reticulum (i.e., reticulin-producing) cells, histiocytes, or other "mononuclear phagocytes." Since a definitive classification is not yet universally available, a category of "unclassified malignant lymphomas" has been retained.

For the sake of consistency, the terms "myeloid" and "monocytoid" have been used for the leukaemias of the granulocytic and monocytic cell series respectively.

In practice, the investigation, diagnosis, and treatment of neoplastic diseases of the haematopoietic and lymphoid tissues are primarily the responsibility of clinical haematologists and pathologists, who have developed their own systems of nomenclature and classification. As a result, a single condition has often been described under a variety of names that do not necessarily convey the same meaning to clinicians who must plan the appropriate and most effective therapeutic regimen. The present classification is the result of a joint effort by both clinical haematologists and histopathologists to resolve many of the misunderstandings that have confused clinicians and hampered controlled epidemiological, biochemical, and

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1 The nomenclature used conforms with that recommended in: Cottier, H., Turk, J. & Sobin, L. (1972) *Bulletin of the World Health Organization*, 47, 375-408. The reticulum cells are those that produce reticulin and form, with the endothelial cells of the lymphatic canals, the architectural "woof". Histiocytes are free cells that are derived from monocytes and are referred to as macrophages when phagocytosis is evident.

therapeutic studies. For such studies uniform nomenclature and classification are essential.

The respective roles of histopathology and cytology in diagnosis are not of equal weight in all the conditions under discussion, but it is important to note that the morphological identification of the component cells of these neoplastic diseases (both systemic and localized) is facilitated by the frequent and routine use of cytological methods that are rarely applied in the identification of tumours of other systems and tissues. In some of the neoplasms listed in the classification, diagnosis depends entirely on histological criteria, while for others a cytological examination is obligatory. Very often the two types of study complement each other, and occasionally neither histopathological nor cytological examination, alone or in combination, can provide a final diagnosis. In such cases, routine methods may have to be supplemented by cytochemical, biochemical, immunological, cytogenetic, electron microscopic, radiological, and/or clinical information.

In general, examination of smears or imprints from aspirated bone marrow and peripheral blood is diagnostic for the leukaemias, while the study of histological sections provides a diagnosis of the localized neoplastic diseases. Both imprints and sections are useful in many of the myeloproliferative and lymphoproliferative diseases. Special studies recommended for diagnosis in specific situations are indicated in the explanatory notes (pages 25-42).

The classification that appears on pages 17-18 has been prepared in order to provide a one-column list of all the neoplastic diseases of the haematopoietic and lymphoid tissues. The neoplasms are grouped in two major categories according to the clinical and gross morphological patterns that prevail. Group I includes those that are systemic diseases, usually without circumscribed tumour formation. Group II includes those in which tumour formation is the usual manifestation but in which there may also be systemic dissemination.

The task of devising an acceptable nomenclature is not an easy one. The descriptive terminology commonly used in systems of tumour nomenclature is an attempt to compress such information into one or two words and can never be more than an approximation to a definition. It is not possible with the available body of scientific knowledge to devise a perfect and definitive nomenclature. The authors are very conscious that many currently used terms, though far from ideal, are sanctioned by long usage and are unlikely to be replaced by new terms, even when the latter would seem to be an improvement. Many of the classical terms that are universally accepted and widely used have therefore been retained even though other terms might be scientifically preferable. Eponyms have been avoided whenever possible, but in a few instances their retention has been necessary.

Considerable difficulty was encountered in classifying the rare diseases. Often the amount of published literature is large in relation to what is
known about the condition, and in some instances experience is limited to a few or even to single cases. Most of these conditions have been included, however, in an attempt to achieve as complete a coverage of the neoplastic diseases of the haematopoietic and lymphoid tissues as possible. It is to be expected that some of the names of rare conditions will disappear in the course of time as knowledge accumulates and new methods of investigation link these conditions with established diseases or permit their reclassification in the light of criteria at present unknown.

The morphological and physiopathological principles proposed by the International Reference Centre have been in part previously published. The present publication is the result of an international collaborative effort and compromise that has resulted in a coordination of various classifications and a unification of nomenclature.

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HISTOLOGICAL AND CYTOLOGICAL CLASSIFICATION OF NEOPLASTIC DISEASES OF THE HAEMATOPOIETIC AND LYMPHOID TISSUES

I. SYSTEMIC DISEASES

A. ACUTE LEUKAEMIAS AND RELATED DISEASES

1. Acute lymphoid leukaemia
2. Acute myeloid leukaemia
3. Acute monocytoid [monocytic] leukaemia
4. Malignant histiocytosis
5. Acute erythraemia (di Guglielmo)
6. Erythroleukaemia
7. Megakaryocytoid [megakaryocytic] leukaemia
8. Acute panmyelosis
9. Acute leukaemia, unclassified

B. CHRONIC LYMPHOID LEUKAEMIA AND OTHER LYMPHOPROLIFERATIVE DISEASES

1. Chronic lymphoid leukaemia
2. Primary macroglobulinaemia (Waldenström)
3. Myeloma
4. Plasma-cell leukaemia
5. Heavy-chain diseases
6. Sézary’s disease
7. Chronic lymphoproliferative disease, unclassified

C. CHRONIC MYELOID LEUKAEMIA AND OTHER MYELOPROLIFERATIVE DISEASES

1. Chronic myeloid leukaemia
2. Variants of chronic myeloid leukaemia
   (a) Neutrophilic leukaemia
   (b) Eosinophilic leukaemia
   (c) Basophilic leukaemia
3. Chronic erythraemia (Heilmeyer-Schöner)
4. Polycythaemia vera (Vaquez-Osler)
5. Idiopathic thrombocythaemia
6. Myelosclerosis with myeloid metaplasia
7. Chronic myeloproliferative diseases, unclassified

D. **CHRONIC MONOCYTOID LEUKAEMIA AND SYSTEMIC HISTIOCYTOID DISEASES**
   1. Chronic monocytoid [monocytic] leukaemia
   2. Histiocytosis X

E. **UNCLASSIFIED LEUKAEMIAS**
   1. Hairy cell leukaemia

F. **OTHERS**
   1. Malignant mastocytosis

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**II. TUMOURS**

A. **LYMPHOSARCOMAS**
   1. Nodular lymphosarcoma
   2. Diffuse lymphosarcoma
      (a) Lymphocytic
      (b) Lymphoplasmacytic
      (c) Prolymphocytic
      (d) Lymphoblastic
      (e) Immunoblastic
      (f) Burkitt’s tumour

B. **MYCOSIS FUNGOIDES**

C. **PLASMACYTOMA**

D. **RETICULOSARCOMA**

E. **UNCLASSIFIED MALIGNANT LYMPHOMAS**

F. **HODGKIN’S DISEASE**
   1. With lymphocyte predominance
   2. With nodular sclerosis
   3. With mixed cellularity
   4. With lymphocyte depletion

G. **OTHERS**
   1. Eosinophilic granuloma
   2. Mastocytoma
CLASSIFICATION HISTOLOGIQUE
ET CYTOLOGIQUE
DES MALADIES NÉOPLASIQUES DES TISSUS
HÉMATOPOÏÉTIQUES ET LYMPHOÏDES

I. MALADIES SYSTÉMIQUES

A. LEUCÉMIES AIGUËS ET MALADIES APPARENTÉES
1. Leucémie lymphoïde aiguë
2. Leucémie myéloïde aiguë
3. Leucémie monocyttaire aiguë
4. Histiocytose maligne
5. Erythrémie aiguë (di Guglielmo)
6. Erythroleucémie
7. Leucémie mégacaryocytoïde
8. Panmyélose aiguë
9. Leucémie aiguë non classée

B. LEUCÉMIE LYMPHOÏDE CHRONIQUE ET AUTRES MALADIES LYMPHOPROLIFÉRATIVES
1. Leucémie lymphoïde chronique
2. Macroglobulinémie primaire (Waldenström)
3. Myélome
4. Leucémie plasmocytaire
5. Maladies des chaînes lourdes
6. Maladie de Sézary
7. Maladies lymphoprolifératives chroniques non classées

C. LEUCÉMIES MYÉLOÏDES CHRONIQUES ET AUTRES MALADIES MYÉLOPROLIFÉRATIVES
1. Leucémie myéloïde chronique
2. Variantes de la leucémie myéloïde chronique
   a) Leucémie à neutrophiles
   b) Leucémie à éosinophiles
   c) Leucémie à basophiles
3. Erythémie chronique (Heilmeyer-Schöner)
4. Polycythémie vraie (Vaquez-Osler)
5. Thrombocythémie idiopathique
6. Myélosclérose avec métaplasie myéloïde
7. Maladie myéloproliférative chronique non classée

D. LEUCÉMIE MONOCYTOÏDE CHRONIQUE ET MALADIES HISTIOCYTOÏDES SYSTÉMIQUES
   1. Leucémie monocytoïde [monocytaire] chronique
   2. Histocytose X

E. LEUCÉMIES NON CLASSÉES
   1. Leucémie à cellules chevelues

F. AUTRES
   1. Mastocytose maligne

II. TUMEURS

A. LYMPHOSARCOMES
   1. Lymphosarcome nodulaire
   2. Lymphosarcome diffus
      a) Lymphocytaire
      b) Lymphoplasmocytaire
      c) Prolymphocytaire
      d) Lymphoblastique
      e) Immunoblastique
      f) Tumeur de Burkitt

B. MYCOSIS FONGOÏDE

C. PLASMOCYTOME

D. RÉTICULOSARCOME

E. HÉMATOSARCOMES [LYMPHOMES MALINS] NON CLASSÉS

F. MALADIE DE HODGKIN
   1. Prédominance lymphocytaire
   2. Sclérose nodulaire
   3. Cellularité mixte
   4. Déplétion lymphocytaire

G. AUTRES
   1. Granulome éosinophile
   2. Mastocytome
ГИСТОЛОГИЧЕСКИЕ И ЦИТОЛОГИЧЕСКИЕ ВАРИАНТЫ ОПУХОЛЕВЫХ ЗАБОЛЕВАНИЙ КРОВЕТВОРНОЙ И ЛИМФОИДНОЙ ТКАНЕЙ

I. СИСТЕМНЫЕ ЗАБОЛЕВАНИЯ

A. Острые лейкемии и родственные заболевания
   1. Острая лимфоидная [лимфобластная] лейкемия
   2. Острая миелоидная [миелобластная] лейкемия
   3. Острая моноцитоидная лейкемия
   4. Злокачественный гистиоцитоз [ретикулез]
   5. Острая эритремия (ди Гутлинемо)
   6. Эритродермия
   7. Мегакариоцитоидная [мегакариоцитарная] лейкемия
   8. Остый панмиелоз
   9. Острая неклассифицированная лейкемия

B. Хроническая лимфоидная лейкемия и другие лимфопролиферативные заболевания
   1. Хроническая лимфоидная [лимфатическая] лейкемия
   2. Первичная макроглобулинемия (Вальденстрема)
   3. Миелома
   4. Плазмоклеточная лейкемия
   5. Болезнь «тяжелых цепей»
   6. Болезнь Сезари
   7. Хронические неклассифицированные лимфопролиферативные заболевания

V. Хроническая миелоидная лейкемия и другие миелопролиферативные заболевания
   1. Хроническая миелоидная лейкемия
   2. Варианты хронической миелопидной лейкемии
      a) Нейтрофильная лейкемия
      b) Эозинофильная лейкемия
      в) Базофильная лейкемия
   3. Хроническая эритремия (Хайлмейер-Шёнера)
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4. Истинная полицитемия (Ваквеза–Ослера)
5. Идиопатическая тромбоцитемия
6. Миелосклероз с миелоидной метаплазией
7. Хронические неклассифицированные миелопролиферативные заболевания

Г. Хроническая моноцитоидная лейкемия и сине-гистоцитоидные заболевания
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3. Leucemia monocitoide [monocítica] aguda
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5. Eritremia aguda (di Guglielmo)
6. Eritroleucemia
7. Leucemia megacariocitoide [megacariocítica]
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4. Leucemia de células plasmáticas
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3. Eritremia crónica (Heilmeyer-Schöner)
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4. Policitemia vera (Vaquez-Osler)
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6. Mielosclerosis con metaplasia mieloide
7. Enfermedades mieloproliferativas crónicas no clasificadas

D. LEUCEMIA MONOCITOIDE CRÓNICA Y ENFERMEDADES HISTIOCITOIDES SISTÉMICAS
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   e) Inmunoblástico
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DEFINITIONS AND EXPLANATORY NOTES

I. SYSTEMIC DISEASES

A. ACUTE LEUKAEMIAS AND RELATED DISEASES

1. Acute lymphoid leukaemia (Fig. 1–6). A systemic proliferation of cells traditionally interpreted as blastic and lymphoid.

While the term "acute lymphoid leukaemia" implies that the cells involved are morphologically homogeneous, significant variations in cell types may be observed and have recently been related to therapeutic sensitivity and prognosis.¹

Common to most types of cells involved in acute lymphoid leukaemia are the following characteristics: a high nuclear-cytoplasmic ratio, a slightly basophilic cytoplasm, an absence of granules, and a high probability of there being only a single nucleolus.

Differences, however, may be seen in cell size, relative amount of cytoplasm, chromatin structure, and distinctness of nucleoli. Among typical "lymphoblastic" cells are some with a diameter greater than 12 μm and a relatively distinct cytoplasm (the so-called macrolymphoblastic variety), and some with a diameter less than 12 μm and an almost imperceptible cytoplasm (the so-called microlymphoblastic variety). Both have a delicate and regularly distributed chromatin and an often indistinct nucleolus.

Another cell type may be observed (the so-called prolymphocytic variety), which appears cytologically more differentiated, the majority of cells showing no distinct nucleolus and a coarser chromatin structure than that observed in blast cells.

A further type may also be seen that appears cytologically so undifferentiated that its designation as prolymphoblastic is tentative; it is appreciably larger than the other three forms, the cytoplasm is more abundant, the chromatin structure is delicately reticulated, and the nucleoli are always distinct. The form of leukaemia associated with such cells is interpreted by some as "undifferentiated" or "stem cell" leukaemia.

The type of acute lymphoid leukaemia characterized by a predominance of prolymphocytes may be difficult to distinguish from leukaemic conversion of prolymphocytic lymphosarcoma and from the prolymphocytic type of chronic lymphoid leukaemia.

While the cells of the preceding types carry either T lymphocyte markers or no markers, a fifth type of acute lymphoid leukaemia, called "immuno­blastic", has been described, composed of cells that are either T or B. ¹ They are large blasts (diameter >15 µm), their nuclei contain a very delicate chromatin, and nucleoli are often visible. Their cytoplasm is more abundant than that in acute lymphoid leukaemias of other cell types, is very basophilic (pyroninophilic), and contains few or many vacuoles.

The primary acute lymphoid leukaemias are those in which the bone marrow is invaded from the very beginning of the disease; this is the main distinctive feature for their differentiation from leukaemic lymphosarcoma (see p. 39).

The histological appearance of the bone marrow and lymph nodes—uniform proliferation of immature cells with delicate nuclear chromatin—may be of diagnostic value; the neoplastic cells of lymphosarcoma are usually more pleomorphic. Histological examination also helps to distinguish the "immunoblastic" type from leukaemic Burkitt's tumour.

2. Acute myeloid leukaemia (Fig. 7–14). A systemic proliferation of immature cells of the granulocytic series in which variations may be due to the degree of cellular differentiation.

Common to most cases of acute myeloid leukaemia are the following cellular features: a relatively abundant cytoplasm, a finely reticulated nuclear chromatin, and usually several distinct nucleoli.

The differences between the several forms of acute myeloid leukaemia pertain particularly to the number and size of granules in the cytoplasm. When granules are evident, the diagnosis is easy. In typical "myeloblastic" leukaemia, they are few and delicate. When they are abundant and relatively coarse, the disease is designated as acute "promyelocytic" leukaemia. When they are absent the disease has sometimes been called acute "promyeloblastic" leukaemia and sometimes "undifferentiated" leukaemia. The presence of Auer bodies establishes the former designation, but their absence does not exclude this diagnosis.

The promyelocytic type is often characterized by major bleeding due to thrombocytopenia and the presence in the serum of fibrin degradation products. These last abnormalities are related to the disseminated intravascular consumption of coagulation factors, with secondary fibrinolysis.

Considerable difficulty is sometimes encountered in differentiating acute myeloid from acute lymphoid leukaemias. The main reason for this difficulty is that in certain cases only a minority of blast cells (at times less than 10%)
are identifiable as belonging to the granulocytic series, while the others either have no distinctive features or may resemble cells of the lymphoid series. The question arises whether the unidentifiable cells are (a) precursor cells of the myeloblast, (b) cells in which granule formation is defective, or (c) blast cells of a different origin, perhaps lymphoid.

In such a diagnostic problem, it has been traditional to seek help from cytochemical procedures. These have been presented in a tabular form by Hayhoe & Flemans¹ and Flandrin & Daniel.² They often confirm and sometimes add to the interpretation based on the nonspecific tinctorial panchromatic features in blood and bone-marrow smears (see colour plate).

Another example of possible mixed cellularity in an acute leukaemia is myelomonocytoid acute leukaemia. In this disease, there is a numerical increase in circulating monocytoïd cells that are morphologically abnormal, while myeloblasts and promyelocytes may prevail in the bone marrow. This type of leukaemia has been classified with the acute myeloid leukaemias although the monocytoïd cells present the typical cytochemical and other characteristics of the monocytoïd series.

Myeloid sarcoma (chloroma) is generally regarded as a variant of acute myeloid leukaemia in which circumscribed tumours precede or are associated with the diagnostic blood and bone-marrow findings of acute myeloid leukaemia. Tumour formation may occasionally occur also in chronic myeloid leukaemia, particularly during blastic crisis (category I. C. 1 of the classification).

Some consider the following types described as I.A.3 and I.A.5–8 as variants of acute myeloid leukaemia. However, they are simply listed here as in most conventional classifications.

3. Acute monocytoid [monocytic] leukaemia (Fig. 15–20). A systemic, progressive, and sustained proliferation of cells immature in appearance and with monocytoïd features. They may be predominantly "monoblastic", "promonocytic", or "promonoblastic".

On the basis of biochemical and cytochemical studies of the acute myelomonocytic leukaemias and in view of recent observations indicating the existence of a stem cell common to granulocytes and monocytes (colony-forming unit on agar), some observers believe that acute myeloid leukaemia, acute monocytoïd leukaemia, and acute myelomonocytoid leukaemia are variations of a single entity. Because of different therapeutic sensitivities of the cells according to their granulocytoid or monocytoïd appearance, the traditional separation has been maintained in the classification.

4. *Malignant histiocytosis* (Fig. 21–23). A systemic progressive and invasive neoplastic proliferation of cells resembling morphologically atypical histiocytes or other mononuclear phagocytes.

In the early phases of the disease the neoplastic cells may look deceptively benign. Phagocytosis, particularly of erythrocytes, may be a prominent feature in the acute disease. The cellular proliferation may be predominantly sinusoidal. It often lacks the cohesiveness of reticulosarcoma and may contain a liberal admixture of inflammatory cells, particularly plasma cells. In the latter phases of the disease, the cell proliferation resembles that of reticulosarcoma. It differs from this tumour by its systemic nature at the time of clinical inception when extensive bone-marrow involvement, generalized lymph node enlargement, hepatosplenomegaly, and constitutional symptoms may be evident and by its usually rapid clinical course. Occasionally, tumour cells appear in the peripheral blood. This disease is also known as “histiocytic medullary reticulosis”.

5. *Acute erythraemia (di Guglielmo)* (Fig. 24). A systemic, progressive proliferation of neoplastic erythroblasts.

This condition has been described as an entity clinically resembling the acute leukaemias. A dissociation between the degree of nuclear and cytoplasmic maturation imparts to the proliferating immature erythroid cells so-called megaloblastoid features sometimes resembling those found in folate or vitamin B₁₂ deficiency. Persistence of these abnormalities after the administration of folic acid or vitamin B₁₂ is essential for the diagnosis of acute erythraemia. The initial abnormal erythroblastic proliferation may continue throughout the course of the disease but there is almost always a gradual increase in the number of immature granulocytes, predominantly myeloblasts, thus producing the haematological picture of acute erythroblastenia or acute myeloid leukaemia.

6. *Erythroleukaemia*. A systemic, progressive, and simultaneous proliferation of immature and atypical cells of both the erythroid and granulocytic series. It exhibits the combined haematological features of acute erythraemia and acute myeloid leukaemia.

The disease may in its course progress into acute myeloid leukaemia without an appreciable participation of the immature erythroid elements. It is often difficult to distinguish erythroleukaemia from acute leukaemia with “reactive” erythroblastic proliferation, but, when the erythroid proliferation is truly neoplastic, the megaloblastoid abnormalities persist following folic acid or vitamin B₁₂ administration.

7. *Megakaryocytoid [megakaryocytic] leukaemia* (Fig. 25–26). A systemic and rapidly progressive proliferation of atypical and poorly differentiated cells of the megakaryocytic series.

Some observers regard megakaryocytoid leukaemia as a variant of
acute myeloid leukaemia in which there is a particularly prominent prolifera
tion of cells of the megakaryocytic series. The few reported cases have
been "aleukaemic" and only rare, if any, identifiable megakaryocytes are
found in the peripheral blood.

8. Acute panmyelosis (Fig. 27-28). A rapidly progressive proliferation of
all three components of the bone marrow, cells of the megakaryocytic series
being particularly prominent. The disease is often associated with thrombo-
cytosis, and platelet aggregates are frequent in blood and bone marrow
smears.

Extramedullary myelopoiesis may be evident in the liver, spleen, and
lymph nodes. Platelet sequestration is a prominent histological feature in
the splenic cords when platelet production is increased. In contrast to
chronic myelosclerosis with myeloid metaplasia, connective tissue (reticulin)
fibres in the bone marrow are only slightly increased or not increased at all.

9. Acute leukaemia, unclassified. A systemic, progressive proliferation of
blast cells in which myeloid, lymphoid, monocytoid, and erythroid morpho-
logical differentiation are not demonstrable.

B. CHRONIC LYMPHOID LEUKAEMIA AND OTHER LYMPHOPROLIFERATIVE
DISEASES

1. Chronic lymphoid leukaemia (Fig. 29-31). A disseminated neoplastic
proliferation of cells with the morphological characteristics of small
lymphocytes (most often of B cell type).

There is usually a pronounced lymphocytosis in the peripheral blood.
The growth pattern and the appearance of the cells in tissue sections in
cases of chronic lymphoid leukaemia are indistinguishable from those in
cases of lymphocytic lymphosarcoma. Therefore an aspiration of a
lymphoid lesion from a patient with lymphocytic lymphosarcoma may
in smear preparations be indistinguishable from chronic lymphoid leu-
kaemia. For this reason bone marrow sections should also be examined
in doubtful cases, bearing in mind that in early chronic lymphoid leukaemia,
the lymphocytic infiltration may be discontinuous, occurring in irregular
though discrete foci in an otherwise normal marrow.

A prolymphocytic variant of chronic lymphoid leukaemia has been
described in which the characteristic cell is larger than the small lymphocyte,
has more abundant cytoplasm, and has a single, very prominent nucleolus,
even when the chromatin is well condensed. Unlike the cells of chronic
lymphoid leukaemia, these cells have abundant surface-membrane-bound
immunoglobulin. Clinically, massive splenomegaly is found, but the lymph

nodes are not enlarged, or are only slightly enlarged. The lymphocyte count almost always exceeds $200,000 \times 10^6$ per litre. Although this type of chronic lymphoid leukaemia resembles histologically the acute lymphoid leukaemia characterized by a predominance of prolymphocytes, it is clinically easy to differentiate from the acute type. It may be more difficult to distinguish from leukaemic prolymphocytic lymphosarcoma.

Recently, a $T$ cell type of chronic lymphoid leukaemia has been described \(^1\) as different from the usual $B$ cell type. It is characterized by massive splenomegaly, a tendency to involve the skin, a positive $\beta$-glucuronidase reaction, and many large azurophilic granules in the lymphocytes (Fig. 31).

2. *Primary macroglobulinaemia* (*Waldenström*) (Fig. 32–34). A progressive and systemic lymphoproliferative disease associated with IgM monoclonal immunoglobulin production.

The proliferating cells, usually found in the bone marrow, spleen, and lymph nodes, appear to be small lymphocytes but may have some features of plasma cells. The macroglobulin may be evident in the cytoplasm and/or nucleus of some of these cells in the form of periodic acid-Schiff-positive globules representing glycoproteins. Occasionally, the histological picture is pleomorphic. Some patients develop what have been called reticulosarcomas, which are more probably lymphoid tumours with pyroninophilic cytoplasm representing \textit{in vivo} "immunoblastic" transformation of the original small lymphoid or lymphoplasmacytoid cells. Tumours having a histological pattern resembling Hodgkin's disease have also been observed. Excessive quantities of IgM of either kappa or lambda type (see Diagrams 1 and 2) can be detected by serum immunoelectrophoresis, and comparably homogeneous polypeptide subunits of these proteins may be found in the serum and/or urine. There is often an associated deficiency in the synthesis of normal immunoglobulins.

IgM monoclonal immunoglobulin may sometimes be found in patients initially diagnosed as having "lymphosarcoma" or "chronic lymphoid leukaemia". Both situations simply represent variants of primary macroglobulinaemia, i.e., a neoplastic proliferation of a $B$ lymphocytic clone in which IgM is secreted in sufficient amounts to be detectable in the patient's serum.

3. *Myeloma* (Fig. 35–36). A systemic neoplastic proliferation of plasma cells, often characterized by the formation of numerous tumours in many bones and multiple fractures. Diffuse infiltration as well as tumours may also occur in the bone marrow and viscera.

The disease is usually associated with IgG, IgA, or light-chain (Bence-Jones) monoclonal immunoglobulin production and the appropriate M

protein or polypeptide is detectable in the serum and/or urine by immunochromic techniques. Occasionally the anomalous immunoglobulin is IgD or even, though rarely, IgE. Myeloma with IgM immunoglobulin has also been reported, but usually this form of monoclonal immunoglobulin production is associated with a lymphoplasmacytoid disease rather than with pure plasma-cell tumours.

In addition to forming circumscribed tumours, the proliferating cells in myeloma may permeate radiologically uninvolved areas in a diffuse fashion that often makes a diagnosis possible from a random marrow examination.

Systemic myelomas may develop after the appearance of apparently solitary bone or extramedullary plasmacytomas (see p. 39). In contrast
to primary systemic myeloma, these metastases frequently produce relatively few but large destructive lesions, often in the fatty marrow of the long bones.

4. **Plasma-cell leukaemia.** A systemic neoplastic proliferation of plasma cells characterized by diffuse infiltration of the bone marrow and associated with monoclonal immunoglobulin production.

The disease differs from multiple myeloma in (1) the consistent presence of circulating plasma cells, (2) the early appearance of bone-marrow insufficiency as in acute leukaemia, (3) the frequent occurrence of generalized lymph-node enlargement, hepatomegaly, and splenomegaly, and (4) the absence of circumscribed bone tumours.

5. **Heavy-chain diseases** (Fig. 37–40). This designation includes (at the time of writing) three monoclonal gammopathies characterized by the excessive elaboration of a portion of the heavy chain (H-chain) of a specific immunoglobulin, usually including the Fc fragment.

In **IgG H-chain disease** (Franklin) the heavy chain of the IgG molecule is demonstrable in the serum and urine. **IgA H-chain disease** (Seligman) occurs in patients with malabsorption syndrome due to diffuse plasma cell infiltration of the small intestine and is often complicated by malignant lymphoid tumours whose appearance is consistent with that of immunoblastic lymphosarcomas. In both these heavy-chain diseases the immunoglobulin-producing cells are plasma cells. **IgM H-chain disease** has been observed mainly in patients with chronic lymphoid leukaemia. A characteristic feature has been the presence of vacuolated plasmacytoid cells in the bone marrow.

6. **Sézary’s disease** (Fig. 41–43). A chronic progressive dermatosis that is characterized clinically by an intensely pruritic erythroderma, haematologically by the presence in the peripheral blood of so-called “Sézary’s cells”, and pathologically by a cutaneous infiltrate composed of atypical “mononuclear” cells.

On the basis of available evidence, it is not possible to determine whether Sézary’s disease is a clinicopathological entity distinct from mycosis fungoides or an erythrodermic variant of mycosis fungoides with circulating atypical “mononuclear” cells. Although the original description of this disease interpreted Sézary’s cells as belonging to the monocytoid histiocytic series, recent studies indicate that they are abnormal T lymphocytes.

7. **Chronic lymphoproliferative diseases, unclassified.** Occasionally a lymphocytic proliferation is difficult to classify as either chronic lymphoid leukaemia or lymphocytic lymphosarcoma. At times, only long-term follow-up makes the diagnosis possible.
C. CHRONIC MYELOID LEUKAEMIA AND OTHER MYELOPROLIFERATIVE DISEASES

1. *Chronic myeloid leukaemia* (Fig. 44-48). A disseminated, progressive proliferation of the cells of the granulocytic series at all stages of maturation.

The cellular proliferation is in most instances entirely granulocytic in type. However, in some cases megakaryocytes and nucleated red cells are found in varying numbers, particularly during the early phases.

Chronic myeloid leukaemia is the only neoplastic disorder that has a disease-specific cytogenetic abnormality, the Philadelphia (Ph¹) chromosome (Fig. 45). This abnormal chromosome is not limited to the granulocytic series but is also demonstrable in erythrocytic and megakaryocytic precursor cells. However, there are rare instances of morphologically typical *chronic myeloid leukaemia in which the Ph¹-chromosome is not demonstrable*. The prognosis in these cases is no different from that in cases of Ph¹-positive chronic myeloid leukaemia. Rather more common are Ph¹-negative cases in which the morphology is not typical, though the atypical features (differential granulocyte count, morphology of granulocytes, frequency of monocyteid cells, and low basophil and platelet counts) are often unrecognized. There is still so much confusion here that a separate name should be allotted to the latter cases. “Atypical chronic myeloid leukaemia” might suffice. The prognosis of this form appears to be worse than the prognosis of morphologically typical chronic myeloid leukaemia. Thus there would be three entities—(1) *chronic myeloid leukaemia, Ph¹-positive*; (2) *chronic myeloid leukaemia, Ph¹-negative*; and (3) *atypical chronic myeloid leukaemia (Ph¹-negative)*.

Tumour formation is sometimes seen in chronic myeloid leukaemia and may involve extranodal sites as well as lymph nodes. In some instances, the clinical manifestations and microscopic features simulate malignant lymphomas, and these cases are often misdiagnosed as reticulosarcomas. The identification of eosinophilic myelocytes and the use of the naphthol-AS-D chloraceta-esterase reaction in tissue sections are helpful in avoiding this diagnostic pitfall.

After a “chronic” course of a few years’ duration, blast cells may appear in excessive numbers and the haematological picture approaches that of acute leukaemia. This is referred to as “*blastic crisis*”. There is a variety in which the blasts are typical myeloblasts and another in which the blasts are small and resemble *lymphoblasts* rather than granulocytes. It is, at times, heralded by an increase of basophilic granulocytes.

2. Variants of chronic myeloid leukaemia

(a) *Neutrophilic leukaemia*. A variant of chronic myeloid leukaemia with a predominance of mature neutrophilic granulocytes in the peripheral blood.

The bone marrow and other organs, however, do not necessarily reflect the leukaemic character of the cell proliferation and are often not suffi-
ciently distinctive to permit a definitive diagnosis. A positive Ph¹-chromosome, if present, establishes the diagnosis.

(b) *Eosinophilic leukaemia* (Fig. 49). A variant of myeloid leukaemia in which eosinophils are predominant.

It is usually seen in a chronic form, and the rarity or absence of immature cells makes it difficult to distinguish this variant from severe reactive eosinophilia. Even when eosinophilic myelocytes are abundant the distinction is difficult. The demonstration of the Ph¹-chromosome is diagnostic. Occasionally an acute form of the disease occurs and blast cells are abundant. These cases are Ph¹-negative.

(c) *Basophilic leukaemia* (Fig. 50). A variant of myeloid leukaemia, usually of the chronic form, in which basophils are predominant.

In basophilic leukaemia there is no problem of confusion with a reactive process as there is in neutrophilic and eosinophilic leukaemias. It should not, however, be confused with the leukaemic variant of malignant mastocytosis. Basophilic granulocytes are peroxidase-positive while tissue mast cells are not.

3. *Chronic erythraemia (Heilmeyer-Schöner)*. A rare, chronically progressive and sustained proliferation of cells of the erythroid series, usually involving the bone marrow and occasionally also the spleen, liver, and lymph nodes.

It is difficult to distinguish this condition from sideroblastic anaemia with marked proliferation of nucleated red cells. The most convincing examples of the disease are those in which widespread visceral erythroblastic infiltrations can be demonstrated.

4. *Polycythaemia vera (Vaquez-Osler)* (Fig. 51). A slowly progressive panmyelosis, characterized by persistent erythrocytosis, leukocytosis, thrombocytosis, increased total red-cell mass, hypervolaemia, and irreversible hyperplasia of the bone marrow in which the cells of the normoblastic, granulocytic, and megakaryocytic series participate.

Polycythaemia vera may often progress to myelosclerosis with myeloid metaplasia, at times to "acute leukaemia" or "blastic crisis", and occasionally to erythroleukaemia or acute erythraemia.

5. *Idiopathic thrombocythaemia* (Fig. 52–54). A chronic, slowly progressive myeloproliferative disease, characterized by a sustained increase of megakaryocytes, an abundant platelet production, and a pronounced thrombocytosis without accompanying neoplastic proliferation of cells of the granulocytic and erythrocytic series.

Disturbances of the clotting mechanism result in a haemorrhagic diathesis and a tendency to vascular thrombosis. Marked sequestration of the platelets in the splenic cords is a characteristic histological feature.
6. **Myelosclerosis with myeloid metaplasia** (Fig. 55–56). A progressive panmyelosis, characterized by intramedullary fibrosis, atypical megakaryocytic proliferation, and myeloid metaplasia in which all three types of myeloid cells are represented.

The metaplasia is usually limited to the spleen, liver, and lymph nodes. Occasionally, involvement occurs at other sites, sometimes with the formation of myelofibrotic tumours. The disease is frequently associated with osteosclerosis, but during the earlier or cellular phase of the disease, fibrosis may be inconspicuous and demonstrable only by means of reticulin stains. A blastic crisis may occur terminally.

Primary myelosclerosis with myeloid metaplasia, as described above, is morphologically indistinguishable from the myelosclerosis that develops in the late stages of polycythaemia vera. However, the term “myelosclerosis with myeloid metaplasia” should not be applied to marrow fibrosis of toxic or infective origin.

7. **Chronic myeloproliferative diseases, unclassified.** Chronic, progressive proliferations of myeloid cells lacking sufficiently clear-cut features to allow differentiation between myelosclerosis with myeloid metaplasia and chronic myeloid leukaemia.

In most instances, fibrosis, or at least an increase in the reticulin fibres of the marrow, is evident. Haematological and histological manifestations in the blood, bone marrow, spleen, and liver may be so variable as to make clear-cut classification impossible. In cases of this type only the presence of the Ph1-chromosome may establish a diagnosis of chronic myeloid leukaemia beyond doubt. If the Ph1-chromosome is not demonstrable or if karyotype analysis has not been carried out, it may not be possible to do more than make a diagnosis of chronic myeloproliferative disease, unclassified.

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**D. CHRONIC MONOCYTOID LEUKAEMIA AND SYSTEMIC HISTIOCYTOID DISEASES**

1. **Chronic monocytoid [monocytic] leukaemia** (Fig. 57–58). A chronically progressive neoplasia of monocytes involving the spleen, liver, bone marrow, and (rarely) the peripheral blood.

Pancytopenia and splenomegaly reflecting a hypersplenic syndrome are the main features of the early phases of the disease. The diagnosis is often made in sections of spleen, removed because of an initial diagnosis of hypersplenism. Histological differentiation from hairy cell leukaemia is difficult unless cytological, cytochemical, and immunological methods are used.

2. **Histiocytosis X** (Fig. 59–64). A progressive proliferation of differentiated histiocytes involving bone, viscera, and skin.

According to the prevailing views, the acute phase, which affects infants and very young children, is identical with **Letterer-Siwe disease**. During
this early phase of proliferative activity the histiocytes contain little or no lipid in their cytoplasm, and the skin infiltrates have a histological appearance that is highly characteristic if not diagnostic. The chronic form, also referred to as Hand-Schüller-Christian disease, is often characterized by single or multiple destructive bone lesions but may also involve the lung, thyroid, lymph nodes, spleen, liver, and (rarely) skin and vaginal mucosa. The proliferating histiocytes in this phase are filled with lipids and resemble foam cells.

E. UNCLASSIFIED LEUKAEMIAS

1. *Hairy cell leukaemia* (Fig. 65–67). A chronic leukaemia in which the circulating leukaemic cells have hair-like cytoplasmic projections.

The projections were first observed by phase-contrast microscopy but are often evident in well-prepared blood smears. Some consider this disease to be monocytoid, but the cells differ from typical monocytes by their weaker esterase activity, by the absence of demonstrable phagocytic activity *in vivo* and in culture and by the presence of an acid phosphatase isoenzyme resistant to tartrate. Some describe them as B lymphocytes, on the basis of membrane immunofluorescence tests.

The most characteristic histological changes are observed in the spleen. The splenic cords are widened by a diffuse infiltration of leukaemic cells, slightly larger than normal lymphocytes. Their precise origin is unknown.

F. OTHERS

1. *Malignant mastocytosis* (Fig. 68–72). A systemic progressive proliferation of atypical tissue mast cells in the haematopoietic organs and in many other tissues.

The disease is rare and may develop in patients who have urticaria pigmentosa. The cells produce both heparin and histamine. Heparin is responsible for the haemorrhagic manifestation of the disease, histamine for flushing of the skin, a sudden drop in blood pressure, tachycardia, hypersecretion of gastric acid, and headaches. The disease is usually aleukaemic, but circulating mast cells may on occasion be found in the blood (“*mast-cell leukaemia*”). The cellular proliferation is morphologically and histochemically readily distinguishable from the predominantly basophilic form of myeloid leukaemia. Outside the skin, the tissue mast cells may be difficult to recognize in histological sections stained by routine methods, but the mast-cell granules are strongly positive with the naphthol-AS-D chloracetate-esterase reaction, which serves as a nonspecific presumptive test for mast cells, subject to confirmation with metachromatic stains such as toluidine blue.
II. TUMOURS

It is not currently possible to propose a scientifically accurate and clinically tested classification and nomenclature of the non-Hodgkin's tumours of lymphoid tissue. The proposed classification therefore contains merely a minor modification of the conventional nomenclature in which the terms "lymphosarcoma" and "reticulosarcoma" were employed. In the subclassification of lymphosarcomas, the term "immunoblastic" is used with the reservation indicated in the footnote on page 13. While lymphosarcomas include only tumours the lymphoid nature of whose cells has either been clearly established or seems very likely, a clear-cut determination of the cell origin of "reticulosarcomas" has not yet been achieved. The term reticulosarcoma is used here for tumours composed of reticulin-producing cells, histiocytes, or other mononuclear phagocytes. This proposed classification, therefore, represents a compromise and is subject to further modifications as new knowledge accumulates on the precise origin of the tumour cells.

A. LYMPHOSARCOMAS

1. Nodular lymphosarcoma (Fig. 73-78). A malignant tumour composed of lymphoid cells arranged in a nodular manner. This tumour, originally named "Brill-Symmers' disease", is considered by some to be of germinal or follicular centre cell origin, and hence composed of B cells. The nodular architecture may be variable in prominence. It may progress to a diffuse pattern. The disease may occasionally become leukaemic.

The cells often have cleaved nuclei and may vary in size. This has been the basis for subclassification of this group of tumours into small, large, and mixed cell types. In well-prepared smears, imprints, or sections the cell population may be prolymphocytic or prolymphocytic and lymphoblastic (lymphoblastoid).

2. Diffuse lymphosarcoma (Fig. 79-92). A malignant tumour composed of lymphoid cells arranged in a diffuse manner.

(a) Lymphocytic. The cells may be lymphocytes (so-called well-differentiated type). In such cases, clinical and haematological examination usually reveals that the patient has a typical chronic lymphoid leukaemia.

(b) Lymphoplasmacytic. The cells may be lymphocytes mixed with plasma cells. In such cases, clinical, haematological, and immunochemical examination usually reveals that the patient has a primary (IgM) monoclonal gammopathy (Waldenström), or occasionally some other form of monoclonal gammopathy (IgG, IgA, light chains only).

(c) Prolymphocytic. The tumour cells may be of the so-called prolymphocytic type, with morphological characteristics intermediate between

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1 The terms "lymphoblastic" and "prolymphocytic" are used because of the resemblance of these cells to those called "lymphoblasts" and "prolymphocytes" in acute lymphoid leukaemia.
those of lymphocytes and lymphoblasts. They may have *cleaved nuclei*. The chromatin is more delicate than that of lymphocytes and coarser than that of blastic cells. The cell population may be *prolymphocytic* and *lymphoblastic* (lymphoblastoid).

*(d) Lymphoblastic.* The cells may be lymphoblastic ¹ (or lymphoblastoid), resembling the macrolymphoblasts, and sometimes the microlymphoblasts, of acute lymphoid leukaemia, but the cytoplasm is very often slightly more basophilic.

In this group are tumours with *convoluted nuclei*, which are usually seen in children and frequently found in the mediastinum.

Data associating certain morphological features with functional characteristics of lymphoid cells are accumulating. The cells of diffuse lymphosarcoma may have B or T or no detectable markers. It is believed that the lymphocytic and the prolymphocytic forms of lymphosarcoma are predominantly of B-cell origin. Many of the lymphoblastic tumours, and particularly those having cells with convoluted nuclei, are believed to be of T-cell origin.

The presence of cells with cleaved nuclei suggests that a diffuse lymphosarcoma is the result of the progression of a nodular lymphosarcoma to a diffuse form. As in the nodular form, the cells vary in size, so that small, large, and mixed cell subtypes may be distinguished.

*(e) Immunoblastic* (Fig. 85–88). A malignant tumour composed of diffusely arranged large lymphoid cells with basophilic (pyroninophilic) cytoplasm containing vacuoles visible on smears or imprints. The nuclei are usually large, may be irregular in shape, and often contain prominent nucleoli. Macrophages are rare, in contrast to Burkitt’s tumour. The tumour cells may have B or T or no detectable markers. The B type may be recognized from the frequency of plasmacytoid features of the immunoblasts. The scarcity of reticulin argyrophilic fibrils helps to distinguish immunoblastic lymphosarcoma from reticulosarcoma.²

*(f) Burkitt’s tumour* ³ (Fig. 89–92). A malignant neoplasm composed of lymphoid cells believed to be of B-cell type with intensive cytoplasmic basophilia (pyroninophilia) and many sudanophilic cytoplasmic inclusions. They are considered by some to be immunoblasts. Macrophages are abundantly interspersed among the tumour cells, forming a so-called "starry-sky" pattern. Although a characteristic histological feature, this pattern is not specific to or pathognomonic of Burkitt’s tumour.

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¹ The terms "lymphoblastic" and "prolymphocytic" are used because of the resemblance of these cells to those called "lymphoblasts" and "prolymphocytes" in acute lymphoid leukaemia.

² Mathé, G. et al. (1975) Immunoblastic lymphosarcoma, a cytological and clinical entity? Biomedicine, 22, 457.

The cells of Burkitt’s tumour are usually smaller than those of immunoblastic lymphosarcoma and usually have 2 or 3 nucleoli, smaller than those of immunoblastic lymphosarcoma.

The presence of Epstein-Barr virus (EBV) genome, which has, with only a few exceptions, been found in typical African Burkitt’s tumour, might prove to be useful in differential diagnosis.\(^1\)

* * *

Lymphosarcoma cells may invade the bone marrow in a diffuse manner. They can be detected by marrow puncture; they may also circulate in the peripheral blood. This “leukaemic conversion” can occur after a non-leukaemic lymphosarcoma phase, which varies from a few weeks or months (early leukaemic lymphosarcoma) to many years (late leukaemic lymphosarcoma).

Morphology can bear an important relationship to prognosis. Patients with nodular lymphosarcoma survive significantly longer, in general, than those with diffuse lymphosarcoma of corresponding cellular composition. The prognosis of the immunoblastic type is most unfavourable, while the prognosis of the prolymphocytic form is better than that of the lymphoblastic form.

B. MYCOSIS FUNGOIDES (Fig. 93–97).

A malignant lymphoid neoplasm that always originates in the upper dermis and is characterized by a pleomorphic cellular infiltrate, probably of the T cell type.

Initially there may be a nonspecific inflammatory infiltrate in which neoplastic cells are either inconspicuous or have a deceptively benign appearance (so-called “premycotic” stage). Intraepidermal aggregates of the neoplastic cells, “Darier-Pautrier micro-abscesses”, are highly characteristic of this disorder. Metastases to lymph nodes and viscera occur in approximately two-thirds of all cases and are histologically distinctive.

C. PLASMACYTOMA (Fig. 98).

A localized tumour composed of atypical and presumably neoplastic plasma cells.

This diagnosis is made with the understanding that either an osseous or an extramedullary plasmacytoma may be a localized manifestation of an

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already disseminated myeloma or the initial manifestation of a plasmacytic tumour that becomes generalized after periods of unpredictable duration. Full radiological, immunological, and biochemical investigations are therefore essential at presentation and during the course of the disease. Some plasmacytomas remain localized. These may either represent truly benign plasmacytomas or plasmacytic pseudotumours (so-called plasmacytic granulomas). The demonstration of monoclonal immunoglobulins in the serum or urine or both may help to establish the neoplastic nature of the disease when the clinical and histological findings are equivocal.

D. RETICULOSARCOMA (Fig. 99–103)

A malignant tumour composed of large cells of uncertain origin which, when showing evidence of the production of argyrophilic fibrils, or phagocytosis, or both, have been interpreted as neoplastic reticulum cells, histiocytes or other mononuclear phagocytes.

The variations in cellular and nuclear shapes are conspicuous. The cytoplasm of the cells is pale and often abundant. Cell borders are distinct and may be accentuated by intercellular argyrophilic fibres that often completely surround the individual cells. The nuclei are either ovoid or indented. The demonstration of lysozyme secretion and fluoride-inhibited nonspecific esterase positivity may help to establish the histiocytic nature of the cells. Progression to a leukaemic phase is exceptional.

Cytological features revealed in Giemsa-stained smears or imprints are helpful in distinguishing between immunoblastic lymphosarcoma and reticulosarcoma. The cells of reticulosarcoma are larger than those of immunoblastic lymphosarcoma and are without prominent cytoplasmic basophilia. Histochemical and immunological techniques (e.g., cell surface markers) may be required for tumour identification.

Primary reticulosarcoma of bone ¹ (Fig. 102–103) is histologically similar to reticulosarcomas arising in lymphoid or soft tissue. Initially, the disease is confined to a single bone, usually a long bone, and is slow to metastasize or spread. After combined radiation and surgical therapy, prognosis is more favourable than with other reticulosarcomas. Histological differentiation from Ewing’s sarcoma (Fig. 104–106) may be difficult, but demonstration of glycogen in the cytoplasm of Ewing’s sarcoma cells, using the PAS reaction, is often of help.

E. UNCLASSIFIED MALIGNANT LYMPHOMAS [HAEMATOSARCOMAS]

Some malignant tumours of lymphoid or histiocytoid cells cannot be classified histologically or cytologically, even from well-prepared sections and imprints. Often problems of classification are enhanced by technical imperfections that make it difficult to assess cellular and nuclear detail with sufficient accuracy. Autopsy sections are particularly unsuitable for accurate classification. Moreover, the presence of more than one cell type—e.g., lymphocytes, histiocytes, and possibly plasma cells—may be confusing. The number of unclassified cases may be increased by the recent introduction of the concept of "immunoblastic lymphosarcoma", which is difficult to distinguish from some reticulosarcomas. It should diminish as soon as the cells of the lymphocyte series can be accurately identified by immunological methods.

F. HODGKIN'S DISEASE (Fig. 107-118)

A malignant neoplastic disease in which typical Sternberg-Reed cells and mononuclear cells with corresponding nuclear features represent the neoplastic elements and in which a variety of inflammatory cells are intimately associated with the malignant cellular proliferation. The inflammatory components of the lesion often form the bulk of the tumour.

The histological picture of Hodgkin's disease shows many variations; these have been consolidated into the following four main histological subtypes.

1. Hodgkin's disease with lymphocyte predominance (Fig. 108-110) is characterized by the abundance of mature lymphocytes. There may or may not be an associated proliferation of well-differentiated histiocytes. This variant corresponds to the "lymphocytic and/or histiocytic type" of Lukes & Butler. Typical Sternberg-Reed cells and mononuclear cells with corresponding nuclear features may be rare. Necrosis and fibrosis are minimal or lacking.

2. Hodgkin's disease with nodular sclerosis (Fig. 111-113) is characterized in its fully developed form by distinct broad bands of collagen subdividing cellular nodules composed of Sternberg-Reed cells, lymphocytes, eosinophilic and neutrophilic mature granulocytes, histiocytes, and plasma cells. So-called "lacunar" cells with abundant pale and often retracted cytoplasm are characteristic of this variant. The nuclei and nucleoli of these cells are often

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smaller than those in classical Sternberg-Reed cells. The collagen is bi­refringent, and bands, which may be inconspicuous in haematoxylin-eosin stained sections, become evident under polarized light. In the cellular form of nodular sclerosing Hodgkin’s disease the fibrous bands are imperceptible but lacunar cells are prominent.

3. **Hodgkin’s disease with mixed cellularity** (Fig. 114) corresponds to what has usually been regarded as the classical picture of Hodgkin’s disease. Although lymphocytes and non-neoplastic histiocytes are still the chief cellular components, Sternberg-Reed cells and mononuclear cells with corresponding nuclear features are more numerous. A wide variety of inflammatory and reactive cells (including eosinophilic and neutrophilic mature granulocytes, plasma cells, and lymphocytes) may be found. Variable amounts of necrosis and fibrosis are seen.

4. **Hodgkin’s disease with lymphocyte depletion** (Fig. 115–118) is characterized by a paucity of lymphocytes. There is either a predominance of neoplastic reticular cells including Sternberg-Reed cells or a diffuse fibrosis.

**G. Others**

1. **Eosinophilic granuloma** (Fig. 119–122). A tumour-like proliferation of well-differentiated histiocytes that lack the morphological features of malignant cells and are often intermingled with numerous mature eosinophilic granulocytes.

   In children, the disease may involve bones as well as extra-osseous sites (usually lymph nodes). In infants and young children, it is usually an early clinical manifestation of histiocytosis X. In adults, the disease tends to be localized, either in a solitary site or in several osseous and extra-osseous locations, and does not necessarily become widely disseminated.

2. **Mastocytoma** (Fig. 123–124). A rare, usually cutaneous tumour of tissue mast cells.

   It occurs as a solitary tumour mass, which may be either a localized manifestation of disseminated mast cell disease or a solitary benign tumour.
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Abbreviations used in the captions to the illustrations reproduced on the following pages:

H & E: haematoxylin-eosin
Giemsa: May Grünwald-Giemsa
Reticulin: silver impregnation for reticulin fibres
PAS: periodic acid-Schiff reaction
**SELECTED CYTOCHEMICAL FEATURES OF THE ACUTE LEUKAEMIAS**

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*The authors gratefully acknowledge the assistance of Dr D. Dantchev, who prepared the artwork for the plate, and Dr G. Flandrin and Dr P. G. Hayhoe, who provided advice and help in the selection of the cytochemical information presented in the table.*
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Bone marrow smear. Giemsa

Fig. 2. Acute lymphoid leukaemia, "microlymphoblastic"
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These very poorly differentiated blast cells resemble lymphoblasts more than myeloblasts or monoblasts. Histochemically they have the characteristics of lymphoid cells
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Bone marrow smear. Giemsa

× 1200

Fig. 10. Acute myelomonocytoid leukaemia

Bone marrow smear. Giemsa

× 1200
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Fig. 95. Mycosis fungoides
A. "Darier-Pautrier microabscess"
Skin section. H & E

Fig. 96. Mycosis fungoides
A. "Darier-Pautrier microabscess"
Skin section. H & E
Fig. 97. Mycosis fungoides
Residual normal lymphocytes (bottom of picture) differ from cells of mycosis fungoides in the upper part.
Lymph node section. H & E

Fig. 98. Plasmacytoma
Section of testis: H & E
Fig. 99. Reticulosarcoma
Lymph node smear. Giemsa

Fig. 100. Reticulosarcoma
Lymph node section. H & E
Fig. 101. Reticulosarcoma
Lymph node section. Reticulin

Fig. 102. Primary reticulosarcoma of bone
H & E
Fig. 103. Primary reticulosarcoma of bone
Reticulin

Fig. 104. Ewing's sarcoma of bone
H & E
Fig. 105. Ewing’s sarcoma of bone
Reticulin

Fig. 106. Ewing’s sarcoma of bone
Glycogen in cytoplasm of tumour cells
PAS
Fig. 107. Hodgkin's disease
Sternberg-Reed cell
Lymph node smear. Giemsa

Fig. 108. Hodgkin's disease with lymphocyte predominance
Lymph node section. H & E
Fig. 109. Hodgkin's disease with lymphocyte predominance
Lymph node section. H & E

Fig. 110. Hodgkin's disease with lymphocyte predominance
Lymph node section. H & E
Fig. 111. Hodgkin's disease with nodular sclerosis
Lymph node section. H & E

Fig. 112. Hodgkin's disease with nodular sclerosis
Typical Sternberg-Reed cells
Lymph node section. H & E
Fig. 113. Hodgkin's disease with nodular sclerosis
Lacunar cells
Lymph node section. H & E

Fig. 114. Hodgkin's disease with mixed cellularity
Lymph node section. H & E
Fig. 115. Hodgkin's disease with lymphocyte depletion
   "Reticular" type
   Lymph node section. H & E

Fig. 116. Hodgkin's disease with lymphocyte depletion
   "Reticular" type. Difficult to differentiate from reticulosarcoma
   Lymph node section. H & E
Fig. 117. Hodgkin's disease with lymphocyte depletion
Diffuse fibrosis type
Lymph node section. H & E

Fig. 118. Hodgkin's disease with lymphocyte depletion
Diffuse fibrosis type
Lymph node section. H & E
Fig. 119. Eosinophilic granuloma
Lymph node section. H & E

Fig. 120. Eosinophilic granuloma
Lymph node section. H & E
Fig. 121. Eosinophilic granuloma
Lymph node section. H & E

Fig. 122. Eosinophilic granuloma
Lymph node section. H & E
Fig. 123. Mastocytoma
Skin section. Toluidine blue

Fig. 124. Mastocytoma
Skin section. Toluidine blue