# OBSERVATIONS ON CERTAIN DISEASES OF THE RETICULO-ENDOTHELIAL SYSTEM.

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PART I. INTRODUCTORY.

GENERAL INTRODUCTION.

The study of the Reticulo-endothelial System has always presented problems to the investigator. Consisting, as it does, of relatively scanty and inconspicuous elements, distributed throughout various organs and tissues, the purely anatomical approach could not yield very fruitful results. It was only when an understanding of the functional activities of the elements began to be achieved, and it became possible to study their structure in relation to their biological actions, that a grasp of the true nature of the various elements and their correlation into a system became possible. The introduction of the aniline series of dyes by Ehrlich, was an important advance which enabled investigators to establish the existence of this distinct system of cells closely related in function. The earlier investigations culminated in the work of Aschoff and Kiyono (1913) who presented a detailed description of the Reticulo-endothelial System, or Reticulo-endothelial Metabolic Apparatus. The biological activities of this system in relation to vital dyes has now been exhaustively studied by many workers and a very complete description was published by Cappel (1929).

In addition to the capacity for storing vital dyes, it was early recognised that the reticulo-endothelial system played an important part in haematopoiesis. This function has been studied by innumerable investigators, notable among whom are Maximow (1909) (1915)(1924), and at a later date, Doan, Sabin and Cunningham, who have/

have published a large series of papers on this subject, commencing in 1920.

Thus a fairly clear understanding of the dye-storing and haematopoietic activities of the system has been achieved.

The Reticulo-Endothelial System as outlined by Intra-vitam Staining.

Cappell (1929) in his work on vital staining, gives an account of the reticulo-endothelial system modified after Aschoff and Landau. This description includes as the reticulo-endothelial system, in the restricted sense, two main groups of cells.

1. The reticulum cells of the splenic pulp and Malpighian bodies, and those of the lymphatic glands and lymphoid tissue generally. These cells are fairly readily stained by vital dyes, but less so than

2A). The endothelial cells which line the lymph sinuses of the lymphatic glands, the sinusoidal blood capillaries of the liver, bone marrow, supra-renal and pituitary glands.

B). The histiocytes or amoeboid wandering cells of connective tissue (clasmatocytes, macrophages etc.). These two groups are very active in storing vital dyes.

C). Certain free mononuclear cells found in the splenic pulp and occasionally in the blood of internal organs. These are generally regarded as being derived from cells of 1, 2A and 2B.

The Fibrocytes or ordinary connective tissue cells also store vital dyes fairly readily, but to a lesser extent than 1, 2A, B or C.

Cappell stresses the close relationship between the reticulum cell and the sinus endothelial cell of the lymphatic glands. Corner(1920) has/

has shown that this type of endothelial cell can produce reticulin fibrils. Cappell (1929) considers that the monocyte may be a phase in development of certain lymphoid cells which is normally passed in the blood stream, and also, that under conditions of stimulation, the monocyte may develop further and act as a macrophage, indistinguishable from histiocytes or from more primitive cells.

There has been some confusion in the use of the term histiocyte, a name put forward by Kiyono (1914), for the relatively large dye-storing cell, found scattered widely throughout the body, and therefore including the reticulum cell, the sinus endothelial cell and the free macrophage. Maximow uses the term in the same way. In more recent writings however, the tendency is to restrict the name histiocyte to the free wandering histioid cells.

The Reticulo-Endothelial System in relation to primitive Mesenchyme, and to Haematopoiesis.

The origin of the white blood corpuscles from the reticulum cell is generally conceded, but the exact stages by which they are derived are in dispute. Controversy has centred chiefly around the existence of a common stem cell derived from the reticulum cell, and giving rise to all three types of white corpuscle. The Monophyletic School postulates a common progenitor for all the blood cells. This cell has been given a variety of names, e.g., Lymphoidocyte, (Ehrlich 1879), (Pappenheim 1898), Haemocytoblast (Maximow 1909). The opponents of this view led by Schilling (1912) consider that differentiation occurs in the embryo/

embryo into the three blood forming tissues, myeloid, lymphoid and reticulo-endothelial (Monocytic). Sabin, Doan & Cunningham (1925) who hold a somewhat intermediate opinion, describe a primitive white corpuscle derived from the reticulum cell, but distinct from the progenitor of the erythrocyte. From this primitive cell they claim to have traced the myeloblast and granular series, the lymphoblast and lymphocytes, and the monoblast and monocyte.

The authoritative views of Maximow (1924) on the origin of the reticulum cell from the primitive mesenchyme and its relationship to haematopoiesis, are of the greatest importance in understanding the disease processes affecting the reticulo-endothelial system, and for this reason it is proposed to consider them at greater length.

According to Maximow, in the foetus, the primitive mesenchyme gives rise to the temporary red corpuscles and secondly to cells which retain their haematopoietic potencies, originally referred to by him as large lymphocytes, but which he later considered to be identical with the haemocytoblast of Ferrata (1918). These cells do not normally produce primitive red corpuscles in extra-uterine life. Maximow also describes histioid wandering cells derived from the mesenchyme of the body of embryo, which are closely related to the haemocytoblast. In adult life these histioid cells or histiocytes, are chiefly fixed in the stroma of the blood-forming organs, whereas the haemocytoblasts are free elements in the blood-forming organs

and/

and the lymph. The histiocytes, may however, give rise to wandering elements. The fixed elements, may remain differentiated and retain their capacity for producing histioid wandering cells or even haemocytoblasts, or they may give rise to fibroblasts. These fixed elements are widespread. Sometimes they form a syncytium, for example in the lymph nodes, the bone marrow and the spleen, where they are intimately connected with the reticulin framework, and are in fact the reticulum cells. Closely allied cells are to be found lining the lymph sinuses of the glands, and the blood sinuses of the spleen. The so-called resting wandering cells of Maximow (1906), clasmatocytes (Ranvier 1900), rhagiocrine cells (Renaut 1907). The fixed reticulum cells including the sinus lining-cells, constitute the reticulo-endothelial system. They may be mobilised to produce the histioid wandering cells, which may multiply and act as macrophages. The fixed cells as well as the free macrophages, may act as phagocytes to a slight extent. and can feebly store vital dyes. Cells with the capacity of storing vital dyes were first clearly defined by Goldmann (1909). who called them pyrrhol cells. Later Kiyono (1914) suggested the general name of histiocytes for such cells.

According to Maximow, histiocytes, in extra uterine life, rarely display their latent haematopoietic potencies, but are easily mobilised and transformed into macrophages. In myeloid and lymphatic tissue, however, new formation of haemocytoblasts from/

from reticulum cells (histiocytes) may occur on rare occasions. Normally histiocytes do not enter the circulation, but may give rise to monocytes which do so. Where histiocytes are lining channels, they may also give rise to monocytes, but they may, themselves, occasionally become free in the blood or lymph. In vitro, lymphocytes may give rise to cells of histiocytic or monocytic type.

Finally Maximow considers that when tubercles form in lymphoid tissue, the epithelioid and possibly the giant cells, are derived from mobilised reticulum cells.

The Distribution of the Reticulo-Endothelial System.

Though there may be some divergence of opinion as to the exact arrangement of the reticulo-endothelial system, there is general agreement upon certain fundamental points. Observers such as Maximow, working from the standpoint of embryology and haematology, have reached conclusions similar to those arrived at by investigators studying the problem from the aspect of vital staining. It may therefore be stated with some confidence that:-

1. In the stroma of the lymphatic glands, spleen and bone marrow, in close relationship to the reticulin framework, there are large irregular cells, the reticulum cells. These cells are only slightly more mature than the primitive mesenchyme from which they are derived, and they possess great developmental potentialities.

2. In the lining of the lymphatic sinuses of the lymph glands, of/

of the blood sinuses of the liver (Küpffer cells), of the blood sinuses of the splenic pulp and in certain of the sinuses of the bone marrow, are situated the so-called sinus endothelial cells, which are however not true endothelium, but are closely related to the reticulum cells and like them are derived from the primitive mesenchyme. These cells have certain developmental potentialities, but tend to differentiate as phagocytes either fixed or free. There is some evidence that they may give rise on occasion to cells indistinguishable from the blood monocyte.

The reticulo-endothelial system may therefore be regarded as composed of reticulum cells and sinus endothelial cells, closely related to one another in their origin from the primitive mesenchyme, and both possessing developmental potentialities. From the former may arise, under abnormal conditions, the whole range of blood corpuscles. On the other hand they may give rise to free wandering phagocytic cells, and finally to the fibroblast and the fibrocyte. The developmental potentialities of the sinus endothelial cell are probably more limited, but it readily becomes phagocytic and may become free. In addition, it may produce the blood monocyte either directly or after first differentiating as a free phagocyte or histiocyte, which has been regarded by certain observers (Damashek 1930) as the precursor of the monocytes, i.e., the monoblast. At certain stages both the reticulum cells and the sinus endothelial cells produce argyrophil reticulin fibrils.

The Reticulo-Endothelial system in disease.

As already described, in efforts to delineate the inconspicuous elements of the reticulo-endothelial system, use has been made of vital dyes and of finely divided particles, for example india ink. Though such substances are useful in demarcating the cells of the system, their presence almost certainly has a stimulating effect, and the appearance of the cells cannot be regarded as typical of completely quiescent normality. Of other methods used to render the cells more apparent, artificial infection with the Listerella monocytogenes has been employed. In this case the appearances are highly artificial. Study of the disease processes naturally affecting the reticulo-endothelial system, although such conditions are far removed from physiological normality, can yield information of importance as to the normal activities of the system.

When subjected to abnormal conditions, the reticulo-endothelial system reacts in two main ways, namely by proliferation of its cells and by differentiation of those cells. Proliferation may, at least theoretically, involve the reticulum cell or any of its derivatives, and varying degrees of differentiation may occur. Consequently, the histological pictures produced in disease of the system, are, at first sight, of great complexity.

In general it may be said that the more acute the process, the greater will be the proliferation, and the less the/

the differentiation, and conversely, in the more chronic processes, differentiation will be more complete, and proliferation less striking. Further, it has been found that the relationship of proliferation to differentiation may vary in different portions of the reticulo-endothelial system during the course of a disease, and the proportions may also vary at different stages of the disease, it is therefore not surprising that a certain confusion of diagnosis has been apt to occur. The study of this group of disease processes, in the light of the modern conception of the reticulo-endothelial system, has yielded considerable information regarding the development and functions of the system.

Classification of Diseases of the Reticulo-Endothelial System.

Formerly in the absence of any clear definition of the structure and functions of the system, and indeed until comparatively recently, in ignorance of its existence, a proper conception of the disease processes affecting it was impossible. Thus it was inevitable that isolated observers should report as separate entities, examples of the same disease, and also that examples of what are now considered to be different diseases, though with similar clinical manifestations, should have been regarded as examples of the same disease process. Broadly speaking the classification of diseases of the reticulo-endothelial system may be considered in three stages. In the first, prior to the introduction of modern methods of haematological/

haematological investigation, and in the absence of any systematised knowledge of the structure and functions of the system, classification was based almost entirely on clinical criteria, and was necessarily inexact. In the second stage, with improved facilities for examination, and with increasing knowledge of the structure and function of the reticulo-endothelial system, classification became more exact, and indeed the tendency was for great elaboration based on histopathological minutiae. On this basis, it appeared that the reticulo-endothelial system might be affected by a very large number of separate diseas processes. In the third, or present stage however, with a fuller understanding, particularly, of the multipotential character of the reticulum cell, it is being realised that many of the apprently different diseases affecting the system are in fact closely related to one another, if indeed some of them are not merely phases of a single disease process. Thus it is probable that the classification of these processes will become simpler as their nature becomes more fully appreciated. At present however, until fuller knowledge is achieved, it is desirable that a fairly detailed provisional classification should be maintained in order that each disease may be defined as accurately as possible, and its relationship to allied processes may then be considered.

One of the earliest orderly classifications was that attempted by Epstein (1924), who distinguished the following types of disease processes in the reticulo-endothelial system.

1./

1. Storage Histiocytomatoses.

2. Histiocytomatoses of inflammatory and proliferative type.
   (A) Limited to the haemopoietic organs.
   (B) Extending to other organs, e.g., Mycoses fungoides, typhoid fever etc.

3. Hyperplastic histiocytomatoses with little tendency to phagocytosis.
   (A) Hyperplasia of endothelial cells.
   (B) Aleukaemic reticuloses.

4. Dysplastic histiocytomatoses (endothelio-sarcoma of spleen, liver etc.)

Although defective in certain respects, and not taking full cognizance of the potentialities of the reticulum cell, this classification has formed a useful basis. Many modifications have been suggested, and that put forward by Oberling and Guerin (1934) represents a distinct advance. These workers took into account the potentialities of the reticulum cell, but their main classification was essentially simple, v.i.z.

1. Storage reticuloses or reticulo-endothelioses.

2. Reticuloses of infective origin.

3. Hyperplastic reticuloses (of unknown origin).

4. Dysplastic reticuloses (tumour formation).

They admit the imperfection of the classification in that, 1. is based on pathogenic, 2 on aetiological, and 3 and 4 on histopathological criteria, but in the absence of exact knowledge as to aetiology in groups 1, 3 and 4, this is inevitable. Ross (1933) gives a more detailed classification which is essentially a histopathological elaboration of that of Oberling and Guerin, v.i.z.

1./

1. Without disturbance of metabolism.

A) Hyperplasia affecting undifferentiated cells, with unrestricted potency for differentiation, i.e., follicular reticulum of lymph glands, Malpighian bodies of spleen and undifferentiated reticulum cells of connective tissue, i.e. true reticuloses.

1. Lymphoid.
2. Fibrillary.
3. Histiocyte.
4. Myeloid.
5. Giant cell.
6. Fibrillary and Giant cell.
7. Unrestricted differentiation or Lymphadenoma.

B) Hyperplasia affecting cells already slightly differentiated, i.e. sinus endothelial or reticulum cells.

1. Leukaemic. Monocytic Leukaemia.
2. Aleukaemic.

II. With altered metabolism.

Hyperplasia of reticulum cells with differentiation to 'Histiocytes' which store various substances (usually lipides) = storage histiocytoses.

Gauchers Disease.
Christian Syndrome.
X Anthomatosis.
Niemann Pick's Disease.
Hypercholesteraemic Splenomegaly.

Robb Smith (1938) suggested an even more elaborate classification based largely on histopathological study of disease processes in the lymphatic glands. His classification was in most respects similar to that of Ross, but he distinguishes 1) processes predominantly affecting the reticulum cells of the lymph follicles, 2)/

2) those affecting the reticulum cells of the medulla of the lymph gland, and 3) those affecting the sinus endothelial cells.

In the present investigation, it is proposed to follow a modified classification combining some features of those already mentioned, v.i.z.

1. Storage Reticuloses. Gaucher's Disease etc.

2. Reactive Reticuloses. a) Sinus Catarrh.

b) Reactive Follicular Hyperplasia.

c) Reactions to Tuberculosis, Syphilis and other Specific infections.

3. Ideopathic Hyperplastic Reticuloses.

A. Acute. 1) Without Differentiation.

a) Reticulum-celled Reticulosis.

11) With Differentiation.

a) Monocytic Leukaemia (Acute type).

b) Histiosyncytial Reticulosis.

c) Histiocytic Reticulosis.

d) Giant-celled Histiocytic Reticulosis.

B. Chronic. 1) Without Differentiation.

a) Giant Follicular Hyperplasia.

11) With Differentiation.

a) Fibrillary Reticulosis.

b) Giant celled Reticulosis.

c) Giant celled & Fibrillary Reticulosis.

d) Unrestricted Differentiation (Lymphadenoma)

e)/

e) Lymphoid Reticulosis.

f) Myeloid Reticulosis.

4. Neoplastic Reticulosis.

A. Reticulosarcomata.

1) Undifferentiated.

11) Reticuloepitheliosarcoma.

111) Reticuloendotheliosarcoma.

B. Dictyocytic Sarcomata.

1) Uniform.

11) Giant cell type.

C. Lymphosarcomata.

1) Lymphocytic type.

11) Lymphoblastic type.

111) Lymphadenoid type (Hodgkin's Sarcoma).

This classification is basically simple, and the subdivisions of each main class are retained for the present in order to correlate the different types of reticulosis. The present study is particularly concerned with groups two and three.

PART II.

Studies of certain diseases of the Reticulo-Endothelial System.

Scope of the Present Investigation.

The present investigation is concerned with the study of disease processes affecting the reticulo-endothelial system, more especially the reactive reticuloses and the idiopathic hyperplastic reticuloses.

Material and Methods.

The material consists of tissues obtained over a period of years, either at biopsy or post-mortem. As far as possible an attempt has been made to correlate pathological and clinical findings. Illustrative examples of the various disease processes are described in some detail, and their significance discussed.

In the routine examination of the tissues, Zenker's fluid was found to be a satisfactory fixative. All tissues were stained by haematonylin and eosin. Eosin methylene blue was also employed, and Leishman's stain was used in some instances for sections, but the results were seldom very satisfactory. Reticulin fibrils were stained by the silver impregnation method of Wilder-Foote. Supravital staining with Janus Green, and neutral red (Cappell 1929) was employed in certain cases, both for impressions of fresh tissue, and for white blood cells; it was seldom however that tissue was obtained fresh enough for the supravital technique to be applicable to impressions. Good-

pastures/

Goodpastures oxydase staining method was also used. The majority of the blood films were stained by Leishman's stain.

Sections were cut as thin as practicable, and in their examination considerable use was made of the 1/12" oil immersion objective. A subsidiary investigation was carried out upon the effects of listerella monocytogenes infection on the reticulo-endothelial system in rabbits.

The Reactive Reticulosis.

a) SINUS CATARRH.

DEFINITION.

A condition characterised by hyperplasia of the sinus endothelial (reticulum) cells, which tend to become free in the sinuses. The hyperplastic cells both fixed and free, but especially the latter, differentiate as phagocytes (macrophages). The condition occurs in glands which drain a focus of irritation, and may occur alone or may be associated with reactive follicular hyperplasia.

EXAMPLES.

This is a very common condition. Figs. 1, 2, and 3 depict a gland draining an area of chronic inflammation in the foot. Figs. 4, 5 are from a gland draining the area of a gastric ulcer. Fig. 6 is of a gland removed during presacral neurectomy in a case of megaloureter with urinary infection. In the first of these Figs. 1, 2, 3, the medullary lymphatic sinuses have been converted into almost solid cords of cells.

In/

In places the sinus endothelial cells can be seen bulging into the lumen. Few of the cells are free in the sinuses. Argyrophil reticulin is prominent in the medullary cords, especially along the walls of the sinuses and fine branches pass among the cells filling the sinuses.

In case 1267 (Figs. 4 and 5) the degree of sinus catarrh was much less striking, the cells formed a delicate network in the lumen, their processes uniting with one another, and with the lining of the sinus. There was no great degree of swelling of the actual sinus endothelium, Fig. 6 is of similar type. No.1788/35 Figs. 16, 17, 18, is another example of sinus catarrh in a gland draining an ulcer bearing area of the stomach. Follicular hyperplasia was also present in this case. In No.60 (Figs. 7 and 8) a gland draining an area of chronic osteomyelitis, numerous fairly large round cells were free in the sinuses, especially the afferent sinus. These cells had a rather darkly staining nucleus rich in chromatin, their protoplasm was relatively scanty and faintly basophilic. They were present in addition to the usual large irregular macrophages. Their exact nature is not perfectly clear, but they resembled, in certain respects, reticulum cells and were probably derived from them. Very similar cells are to be seen in L. monocytogenes infection in rabbits, and there is some evidence that some of them are closely allied to, if not identical with monocytes. Fig. 9 is from a gland draining the bowel/

bowel, in a case of dysentery and shows an open type of sinus catarrh with macrophages and numerous large free cells, of the type described above, in the sinuses. Figs. 10 and 11 depict a gland from the para-aortic group removed during operation upon a vertebral chondroma. They show a gland of the haemolymph type. The sinuses of both cortex and medulla were full of red corpuscles and in the sinuses there were numerous macrophages, many of which were free and distended with red cells. Some similar, large erythrophagocytic cells were also present in the medullary cords, and even in the cortical follicles, in these latter situations, they were apparently fixed, and were stellate in outline. This is regarded as the normal appearance of a haemolymph gland and is an expression of the phagocytic potencies of the sinus endothelium and of macrophages derived from the reticulum cells.

COMMENT.

Sinus catarrh is interpreted as the reaction on the part of the sinus endothelial (reticulum) cells to a comparatively mild irritant. The sinus endothelial cells and the branching reticulum cells of the sinuses swell up and tend to assume a more rounded form. They may or may not become free in the lumen of the sinus as macrophages. The sinus endothelial cells are there considered to be undergoing differentiation ot phagocytes either fixed or free.

b) REACTIVE FOLLICULAR HYPERPLASIA./

b) REACTIVE FOLLICULAR HYPERPLASIA.

DEFINITION.

A condition characterised by hyperplasia of reticulum cells, especially of the cortical follicles and to a less extent of the general basic reticulum cells of the lymphatic glands. Almost invariably accompanied by some degree of cararrh of the lymph sinuses. The condition occurs either locally in the glands draining a focus of irritation or generally e.g., in glandular fever.

EXAMPLES.

The condition constitutes the reaction to a wide variety of irritants, thus in the present series No. 732,Figs. 12-15 was a gland which drained a cancerous breast. There was no evidence of metastatic deposits, but the histological picture was characteristic of reactive follicular hyperplasia. No. 1788, Figs. 16,17,18, was a gland draining the area of a gastric ulcer, which was removed during partial gastrectomy. No. 253,Fig. 19 was a gland draining an area of chronic pyogenic infection of the neck. Figs. 20 and 21 also represent typical examples of reactive follicular hyperplasia. The more generalised form is represented by Fig. 171 from a case of probable glandular fever. In this case which occurred in the Middle East, the disease was characterised clinically by an acute onset with fever, headache, malaise and generalised muscular pains. Some general glandular enlargement was present.

The duration of pyrexia was short, but glandular enlargement persisted for a considerable time. The exact nature of the febrile illness is uncertain, but though classed as Pyrexia of uncertain origin, and though there was only a slight relative lymphocytosis, there is a strong probability that it was in reality a type of glandular fever, a disease which was constantly being met with in small outbreaks. The prolonged persistence of glandular enlargement was however unusual. Pratt (1931) records rather similar appearances in cases of undoubted glandular fever.

DESCRIPTION.

The condition of reactive follicular hyperplasia characteristically presented the following features.

The lymphoid follicles were mainly large, numerous and well defined. Figs. 12-23. There were also a number of small so-called secondary follicles. Typical small lymphocytes were compressed to form a rim around the enlarged follicles. Similar lymphocytes were more loosely arranged throughout the inter-follicular stroma of the gland, and also throughout the medullary cords. The central, lighter part of the follicle, was composed of larger cells, their protoplasm was fairly copious, and in many, the cell body was prolonged into blunt processes giving a rather stellate appearance. The protoplasm was faintly basophilic. The nucleus was large, with rather delicate chromatin, and there was a clearly defined dark staining nuclear rim; a nucleolus was generally present. Among the compressed/

compressed peripheral lymphocytes a few large cells,with the characteristics of basic reticulum cells,were to be seen. Mitotic figures were extremely scanty in the reticulum cells, and were absent in the lymphocytes. There was practically no evidence of phagocytic activity to be made out. Blood capillaries were infrequent in the hyperplastic follicles. Argyrophil reticulin fibrils were completely absent in the central portions of the follicles, but occurred in fine strands, rather compressed together among the peripheral lymphocytes, Fig. 15. Large branching reticulum cells were also numerous in the medullary cords. In this situation there was the normal amount of reticulin. The endothelial cells of the lymph sinuses of the cortex and medulla were in places swollen and projected into the sinuses in which some were free as macrophages.

Comment.

Reactive follicular hyperplasia is interpreted as a reticulosis, i.e., a hyperplastic process involving the basic reticulum cells of the glands not only in the follicles, but to a lesser extent throughout the stroma of the cortex and medulla of the glands. The hyperplasia is however of an orderly type, and of moderate degree and the normal architecture is retained and indeed exaggerated. The exact significance of this type of hyperplasia has never been clearly defined, as the reticulum cells exhibit little or no phagocytic activity. In the present investigation it has been the rule for some degree of sinus

catarrh/

catarrh to be associated with reactive follicular hyperplasia, phagocytic activity has been mainly if not entirely confined to the sinuses and the reticulum cell hyperplasia has apparently been a concomitant. It is noteworthy that the irritants which give rise to follicular hyperplasia are of a comparatively mild type, and that the reaction represents the result of such a mild irritant applied for a fairly prolonged period. Very acute inflammatory processes on the other hand give rise to polymorphonuclear infiltration, and even abscess formation, in the associated glands. It would seem therefore, than in reactive follicular hyperplasia, the irritant on reaching the gland leads to catarrhal changes i.e., phagocytic activity and hyperplasia of sinus endothelium, and goes on to stimulate the basic reticulum cells to proliferate, few of these cells however, differentiate as macrophages, though some may become free. Should the irritant become more dangerous, the reticulum cells are fully prepared and are in a position to produce macrophages in large numbers. Support is given to this view by the changes which take place in the lymphatic glands of rabbits in experimental **L.** monocytogenes infection (infra).

Whether a gland which has been the seat of reactive follicular hyperplasia can return to its normal state, is doubtful. If the degree of hyperplasia is slight, it is possible that it may do so but in more advanced examples it appears, that a proportion at least of the reticulum cells mature to fibroblasts and fibrocytes, and that the gland ultimately becomes/

becomes largely fibrosed. Such a fibrosed state is frequently met with in the groin glands of adults, which have been subjected to repeated minor irritation. In experimental L. monocytogenes infections, where there is a considerable reticulum cell hyperplasia, in the later stages, some of the reticulum cells of the follicles assume the appearance if fibroblasts (infra).

c. REACTION TO TUBERCULOUS INFECTION.

No. 1717 Figs. 22-26 was at an early stage of tuberculous involvement of a lymphatic gland. The gland was the seat of sinus catarrh and of follicular hyperplasia and, at the same time, the central reticulum cells of some of the cortical follicles were becoming eosinophilic and in certain areas were beginning to fuse together forming multinucleated plaques. In a few areas there were typical tubercle giant cells. Around the periphery of the affected follicles there was a rim of small lymphocytes. Argyrophil reticulin fibrils were present in considerable amount in the affected follicles, where the fibrils passed among the cells of the tubercle follicle. There was rather more reticulin than normal in the medullary cords, and it was also to be seen branching among the hyperplastic cells in the medullary sinuses. No. 890, Figs. 27-29, shows a later stage in the reaction to tuberculous infection. The cortical follicles were almost entirely occupied by changed reticulum cells. There was also great hyperplasia of the sinus endothelium. Reticulin fibrils were copious throughout the tuberculous/

tuberculous tissue, but scanty among the peripheral lymphocytes. The fibrils were coarsest at the periphery of the follicles, whence finer branches passed towards the centres. They were also prominent at the sides of the solid cords of cells, in the medullary sinuses, whence branches passed among the cells. In No. 909, Figs. 30-31 the tuberculous process was more advanced. The gland was largely composed of young fibrous tissue amongst which reticulin fibrils were very copious, the fibrils being relatively coarse. There were also areas of caseation around which the reticulin was aggregated; towards the centres of the caseous areas the reticulin fibrils had been destroyed.

At an even later stage, where almost the whole gland was caseous, No. 992, Fig. 32, reticulin fibrils persisted around the caseous areas, and also around the inside of the fibrous capsule of the gland. Passing into the caseous areas, blunt processes of reticulin were to be seen, which disappeared as the deeper portion of the caseous area was reached.

SIGNIFICANCE OF THE REACTION TO TUBERCULOUS INFECTION.

From these examples of tuberculous adenitis, it appears that the first reactions of the gland is a stage of sinus catarrh and follicular hyperplasia. In some instances indeed, the sinuses become distended and converted into solid cords, the so-called 'Endothelial tubercle'. At a slightly later stage some of the follicular reticulum cells, undergo changes, being converted/

converted into the "epithelioid cells" of the tubercle follicle, and the tubercle giant cells. The change, from reticulum cell to epithelioid cell, is peculiar in as much as the epithelioid cells do not resemble at all closely, the ordinary phagocytic cells produced in other infective conditions. In the process of change the reticulum cells produce reticulin fibrils and, even when caseation occurs, these fibrils are resistant to the liquefactive process. Later the gland becomes largely fibrous or caseous, and in either case, but especially in the former, reticulin formation is very copious. The tuberculous process may be considered in two stages. In the first the gland displays the normal reaction to irritation, viz. sinus catarrh and follicular hyperplasia. Should the infection persist the already hyperplastic reticulum cells react, largely in the direction of fibril formation, first producing reticulin fibrils, and later becoming changed to fibroblasts which ultimately produce collogen fibres thus endeavouring to localise the remains of the tuberculous process. Instead of total fibrosis areas of caseation may occur and persist either as caseous material or calcified foci among the fibrous tissue.

In other conditions involving reticulum cell proliferation, notably in the Hodgkin group of diseases, reticulin and giant cell production are also met with, and in the later stages fibrosis occurs; thus there are certain parallels between the tuberculous process and the Hodgkin type of/

of process, but there are important differences. The type of giant cell is different. In the former there is evidence that it is formed by coalescence of several cells, whereas in the Hodgkin's Group, it is formed by nuclear division, and is entirely different in appearance from the tuberculous type. Recognizable epithelioid cells are not met with in Hodgkins Disease. Caseation is very rare. The whole process in the Hodgkin Group is of a more diffuse and less focal character, and the preliminary stages of sinus catarrh and follicular hyperplasia do not occur. In simple reactive hyperplasia, although there may be considerable hyperplasia of follicular reticulum cell, reticulin formation is negligible.

Sarcoidosis. The position occupied by this condition among the diseases affecting the reticulo-endothelial system, is by no means clear. The chief question is whether sarcoidosis is to be regarded as a specific granuloma or rather as a bizarre reaction to infection with the tubercle bacillus.

Sarcoidosis may be described as a systemic disease affecting particularly the lympho-haemopoietic apparatus i.e. a reticulo-endotheliosis, with the formation of folliculoid granulation tissue. The lesions tend to regress spontaneously giving a picture of slow development and benign protracted course.

No example of distinct sarcoidosis has been met with in the present study. Cameron and Dawson (1942) in an extensive review of the subject describe the clinical features and histology/

histology as follows. The characteristic clinical manifestations are:-1. Multiple lymphadenopathy. 2. Extensive radiological changes in the lungs with little or no clinical disturbance. 3. Bone marrow and bone changes with osteoporotic lesions of the hands and feet. 4. Splanomegaly. 5. Iridocyclitis. 6. Skin involvement by the typical issue. The tissue consists of epithelioid cells arranged in follicles. There is little or no necrosis, a variable number of multinucleated giant cells may be present, and there is a surrounding aggregation of lymphocytes. Regression is by fibrosis and hyalinisation. The ordinary laboratory criteria of tuberculosis viz. the presence of tubercle bacilli in the sputum, - intradermal tests and animal inoculation are almost always negative. Schaumann (1936), who formerly favoured the hypothesis of a specific granuloma, now considers that the evidence in favour of a tuberculous origin is very strong. The condition resembles in many respects chronic miliary tuberculosis which was described at length by Hoyle and Vaizey (1937).

OBSERVATIONS ON THE REACTIVE RETICULOSES.

From the foregoing observations it appears that the earliest reaction on the part of lymphatic glands, to an irritant, is hypertrophy of the sinus endothelial (reticulum) cells which may remain fixed or may become free, both fixed and free cells being capable of phagocytic activity. This constitutes the common picture of sinus catarrh and though the appearance of/

of the lymphatic sinuses varies, from solid cords of hyperplastic cells, to an open arrangement with numerous free phagocytes, the process is fundamentally the same. If the cells remain fixed in solid cords, they may produce reticulin fibrils (Corner 1920). As well as the large cells with pale nucleus and eosinophilic protoplasm, which are actively phagocytic in the lymphatic sinuses, another type of cell with regular outline, round rather darker nucleus and faintly basophilic protoplasm, is frequently met with. This cell has not been observed to be actively phagocytic, although it appears in response to an irritant, and a clearly similar cell is met with in large numbers, in the lymphatic sinuses of the glands of rabbits stimulated with listerella monocytogenes, its exact nature is not perfectly clear, but it bears some resemblance to the monocyte, and indeed in appearance, is intermediate between the hyperplastic fixed reticulum cell and the monocyte. Very similar cells were met with in many other conditions, notably in certain of the reticuloses such as No. 125, where there was also hyperplasia of the sinus endothelium. It must be emphasised, that the large macrophages of the lymph sinuses and of the splenic blood sinuses, which can often be seen filled with red corpuscles, differ very considerably in appearance from the sinus endothelial cells. This is particularly noticeable after stimulation with L. monocytogenes Fig. 153 where also the pale vesicular nucleus and copious irregular eosinophilic protoplasm are in contrast/

contrast to the other type of free cell, which appears to arise mainly from the true reticulum cells of the glands.

The next response to irritation is reactive follicular hyperplasia where the true reticulum cells become involved, and are in readiness to produce phagocytic and mobile cells. They can also produce, not only the epithelioid cells, but also the giant cells of the tubercle follicle, as has already been described. Analagous reactions may occur in the spleen, and hyperplasia of the sinus endothelium with free cells, both of the macrophage type, and of the smaller monocyte-like type, is frequently recognised. Experimentally, after stimulation with L. monocytogenes, these features become very apparent, and in addition, there is hyperplasia of the true reticulum cells of the Malphighian bodies comparable to the hyperplasia which occurs in the true reticulum cells of the lymph glands.

## IDEOPATHIC HYPERPLASTIC RETICULOSES.

### DEFINITION.

Processes characterised by an overgrowth of reticulum and, or sinus endothelial cells or of their offspring, occurring in the absence of any ascertainable causal factor, such as infection, and not presenting the characteristics of malignancy as generally understood. This group, therefore, includes a wide variety of processes, which however may be considered in two main sub-groups, v.i.z. the acute reticuloses and the chronic reticuloses.

### ACUTE RETICULOSES.

Cases 101/39, 19/46, 125, 264, 16512 are considered to be examples of this sub-group. The main clinical features of these cases are summarised in Tables I and II.

Clinically the acute reticuloses are characterised by an acute febrile illness associated with a varying degree of glandular enlargement. Sometimes the glands are quite small and discrete, and sometimes very large forming matted masses. In general however they tend to be relatively small. The spleen in invariably enlarged, but seldom greatly so, and the enlargement does not appraoch that seen in chronic myeloid leukaemia. Progressive anaemia is the rule, and in the later stages purpuric manifestations are common; in fact there is a haemolytic anaemia and a moderate degree of jaundice may occur. Jaundice is in general more severe in the acute reticuloses of infants/

infants (Oberling and Guerin 1934), but was striking in two of the present cases. The duration of these diseases is variable, but is seldom more than three months at the most.

PATHOLOGY.

The post-mortem appearances are not particularly characteristic.

Apart from glandular enlargement, moderate splenomegaly, and in some cases slight hepatomegaly, the features are those of an acute haemolytic anaemia. There may be some areas of whitish infiltration visible in the liver or kidneys and the bone marrow, which is in general pale, may present areas of whitish tissue. The lymphatic glands are soft, and on section the cut surface tends to bulge. It usually shows small red haemorrhagic flecks. The spleen is also soft and the Malpighian bodies are indistinct.

HISTOLOGICAL APPEARANCES.

No. 101/39, Figs. 33-42, is regarded as a typical example of acute reticulosis without differentiation. The fundamental process in this case was a hyperplasia of the reticulum cells. In the lymph glands the normal structure was obscured by these hyperplastic cells. There was little if any attempt at differentiation. The type cell was large with relatively copious neutrophilic protoplasm. The cell outline was distinct. The nucleus was round or indented, and relatively pale, the chromatin being arranged either in a few strands radiating from the single nucleolus, or in some instances consisting of fine/

fine scattered granules in the nucleus. The cells were very uniform and mitotic figures were frequent. In the lymph sinuses there were a few large irregular macrophages, which showed erythrophagocytosis. There was a similar uniform cellularity of the bone marrow. In the spleen the malpighian bodies were small, with a few remaining lymphocytes in the central part, surrounded by large cells similar to these in the lymph glands and bone marrow. The splenic pulp was stuffed with the typical cells.

The suprarenal glands were extensively infiltrated by the type cells. There was also some infiltration of the kidneys especially along the blood vessels beneath the capsule. There was no infiltration of the liver.

Case 19/46, Figs. 43-46 was that of a woman aged 57 years. There was no abnormality of the white cells in the peripheral blood. Histologically there was overgrowth of reticulum cells, and in addition there were great numbers of large eosinophilic cells free in the sinuses of the lymph glands, carrying on erythrophagocytosis. These cells were frequently laden with red corpuscles and sometimes with brown pigment. By far the greater proportion of erythrophagocytosis was going on in the sinuses, very little was to be seen in the trabeculae of the gland. It was noteworthy that profound anaemia of haemolytic type was a feature in this case. The duration of the disease was somewhat/

somewhat longer than is usual, and in some areas the appearances were of early fibroblast formation, suggesting that differentiation was occurring in at least two directions, v.i.z. to macrophages and to fibroblasts. In No. 125 Figs. 47-51 there was only a moderate overgrowth of reticulum cells, and a large number of lymphocytes remained. There was considerable erythrophagocytosis by large cells in the lymph sinuses. The sinus endothelial cells were also swollen, and apart from the phagocytic cells, there were many large cells free in the sinuses. These cells had faintly basophil protoplasm, relatively large nuclei and resembled in their characteristics monocytes. In this case there was no apparent increase in monocytes in the peripheral circulation. Anaemia was progressive and severe. No. 264 Figs. 52-53 was regarded clinically as an example of monocytic leukaemia as the monocytes in the peripheral blood were greatly increased in number, and some of them were regarded as being immature or monoblasts. The total leucocytes were not increased.

The histological picture however was quite different from that of 16512 which was also considered to be an example of monocytic leukaemia. In the lymph glands and spleen there was a moderate degree of reticulum cell hyperplasia and scattered among the other cells there was a considerable number of large free round cells, with the characteristics of monocytes. A small amount of erythrophagocytosis was present in/

in the lymph sinuses, and a very considerable amount in the splenic sinuses. This case is regarded as an acute reticulosis with some differentiation to monocytes which were escaping in moderate number into the peripheral circulation. Histologically there was some resemblance to No. 125.

ACUTE RETICULOSIS WITH MONOCYTIC DIFFERENTIATION.

Case 16512 is a typical example of what is usually described as monocytic leukaemia. At the same time it presents the characteristics both clinical and histological of an acute reticulosis.

The patient, a male aged 24 years, suffered from an acute febrile illness of two months' duration. There was moderate generalised glandular enlargement, most apparent in the cervical region. Splenomegaly was of moderate degree. Profound progressive anaemia occurred and shortly before death purpuric manifestations made their appearance. The leucocyte count rose from 76,000/CMM to 200,000/CMM. with from 62% to 77% large mononuclears. The large mononuclears of the blood were of the usual type with fairly copious rather greyish-blue cytoplasm. The nucleus was large, usually indented, with the chromatin arranged in fine interlacing strands. One or more nucleoli were present in a proportion of the cells. Some of the cells, particularly those with nucleoli, had an irregular outline with blunt pseudopodia-

like/

like processes, and in many of the cells the protoplasm was vacuolated. The oxydase reaction was negative.

The histological picture in the various organs was very characteristic, especially in the lymphatic glands and spleen. In the former there was intense hyperplasia of the reticulum cells throughout the whole gland, though the process was more advanced in the medulla and inter-follicular cortex, whence the hyperplastic cells could be seen invading the lymphoid follicles, replacing the lymphocytes, Fig. 54 in the main the hyperplastic reticulum cells were joined together by delicate processes.

The endothelial cells of the lymph sinuses were also greatly increased in number and were swollen, their nuclear characteristics closely resembling those of the reticulum cells. The majority of both types of cell had a nucleolus. Many of the nuclei were indented and showed a fine chromatin network, so that they were very reminiscent of the nuclei of the monocyte. Many free cells with the characteristics of monocytes were free in the lymph sinuses, in the substance of the gland, and in the blood vessels of the gland and of its capsule Figs. 55-56. In the spleen the malpighian bodies were indistinct, and were composed of a few lymphocytes with many larger cells of monocytic type especially towards the periphery of the malpighian body, Fig. 58. The splenic sinuses contained relatively little blood, and the endothelial cells/

cells were greatly swollen giving the splenic pulp a solid texture. The swollen endothelial cells of the sinuses had the same appearance as the swollen endothelial cells of the lymphatic sinuses. Many cells with the characteristics of monocytes were free in the splenic sinuses. The bone marrow Fig. 57 showed a similar overgrowth of reticulum cells, with numerous monocytes. In the liver Fig. 59 there was a rather diffuse infiltration with monocytic cells. Erythrophagocytosis was occurring in the splenic sinuses, but was not a prominent feature. The essential process in this case was hyperplasia of the reticulum and sinus endothelial cells, with differentiation to monocytes which were greatly increased in the peripheral blood stream.

Comment on Monocytic Leukaemia.

It was the recognition of the monocyte as a third distinct type of white corpuscle by Schilling (1912) that led to the recognition and description of monocytic leukaemia as a separate entity by Resehad and Schilling (1913). Until recently the disease was regarded as a rarity. Gittins and Hawksley (1930) were able to collect from the literature only 21 cases supported by histology. Since then however it has apparently been more frequently recognised, especially in the U.S.A., and Evans (1942) accepts 179 cases from the literature, but admits that in a proportion the diagnosis was not supported by autopsy. There is still a body of opinion which denies the existence of monocytic leukaemia as a separate entity/

entity and considers it to be merely a phase of the myeloid or lymphatic type. Evans (1942) in a questionnaire to 45 haematologists, found that of 40 who replied, 34 believed in its occurrence, 2 did not, and 4 gave no opinion. Its frequency in relation to other forms of leukaemia varies from clinic to clinic. From personal experience over the past 15 years, it would appear to be extremely rare. Cases have been described at all ages and both sexes, but it is commoner in males between the ages of 20 and 40. The onset is usually abrupt. Ulcerative lesions of the gums and throat are a common early feature, and have led to a suspicion of agranulocytic angina in some cases. As might be expected, in this condition buccal infection is often precipitated by dental treatment, especially removal of teeth, and this may call attention to the disease. Enlargement of the lymphatic glands is usually only of moderate degree, and is sometimes localised to the cervical glands, draining the buccal cavity (Forkner 1936). The splenic enlargement is stated to be as a rule midway between that occurring in lymphatic and in myeloid leukaemia. The liver also is generally enlarged. Skin lesions are frequent, and consist,in the earlier stages, of small plaques which may become ulcerated, and which are composed of aggregations of monocytes (Whitby & Christie 1935). (Osgood 1937). In the earlier stages of the disease the granulocytic series of cells is not much affected, but with extensive involvement of the marrow, these cells are reduced

in/

in numbers, and young forms may occur in the peripheral blood. High irregular fever is the rule in acute cases. Anaemia is progressive and is associated in the later stages with purpuric manifestations. The usual duration of the disease from the time of diagnosis till death, is from 3-6 weeks. (Evans 1942), (Damashek 1930). A subacute and a chronic form of the disease have been described, Laurence, Josey & Young (1931) record a case with survival for fifty six weeks, and Osgood (1937) one lasting two years.

The nature of the monocyte found in the blood in monocytic leukaemia, has been the subject of controversy. Most authors consider it to be identical with the ordinary blood monocyte, but Damashek (1930) considers that a proportion of the monocytes in a case recorded by him were histiocytes. These cells were different in appearance from the usual monocytes, in that their nucleus was round or oval, with relatively coarse chromatin, forming a coarse network, their protoplasm was greyish blue, with numerous vacuoles and pseudopodia were common. A few contained ingested red corpuscles. Damashek refers to them as histiocytes or monoblasts or immature monocytes. He further states that nucleoli are not present in the monocytic series of cells. Gittins & Hawksley (1933) describe nucleoli as scanty and indefinite. Evans (1942) states that nucleoli are usually present.

There/

There have been a considerable number of reports on the histological appearances in monocytic leukaemia. (Ugruimow (1928) describes the splenic pulp and liver as being full of large cells, the Kupffer cells of the liver as increased and often containing red corpuscles. Also he noted islands of cells of the monocyte series in the bone marrow.

Schwirtschewskaja (1928) describes distension of the sinuses of the splenic pulp by large cells and hyperplasia of the reticulo-endothelial cells in the spleen, lymph nodes and marrow. In his case the Kupffer cells were normal. Gittins & Hawksley (1933) noted that the lymphatic glands were very cellular, the cells being of various sizes and shapes, but apparently of the monocytic series. They considered that the cells were being produced from lymphatic reticul-endothelium. In their case the Malpighian bodies of the spleen were small and scattered among the remaining lymphocytes were monocytes. In the splenic pulp the number of monocytes was very great, and they were scattered indiscriminately. Evans (1942) describes infiltration of the organs and tissues with monocytes and general reticulum cell hyperplasia. In the so-called chronic form of monocytic leukaemia the histological features are said to resemble closely those of lymphadenoma (Osgood 1937), (Doan, Wiseman Cunningham 1934).

Hittmair/

Hittmair (1942) takes the view that there are two forms of monocytic leukaemia. In the first, following the teaching of Naegli, he considers that the monocytes are derived from myeloblasts. This type of case is invariably acute and to justify a diagnosis of monocytic leukaemia, at least 50 per cent of the white cells must be monocytes. The majority of such cells are stated to be oxydase positive, and with supravital staining show neutral red rosettes. In this type of monocytic leukaemia the histological appearances are said to be those of any acute leukaemia but most closely resemble the myeloid type. Such cases usually become frankly myeloblastic at some period of their course, and the blood picture may vary from time to time, being sometimes monocytic and sometimes myeloblastic. The existence of such a type of leukaemia affords an explanation of the type of case described by Bloom (1928), where the blood picture varied from myeloblastic to monocytic. At the same time it is difficult to accept as frankly monocytic, a case, where the fundamental change appears to involve the myeloid series. Its recognition depends upon acceptance of the view that the monocyte may be derived from the myeloblast, a cell which more generally gives rise to the granular series.

The second type of monocytic leukaemia is described by Hittmair, as leukaemic reticuloendotheliosis. This may be acute or chronic and is said to be rare in women. Frequently/

Frequently 70-90 % of the white cells are monocytes. Hittmair states that immature monocytes (monoblasts) may be found and that a proportion of basophil mononuclear cells intermediate between the haemocytoblast and the reticuloendothelial leucocyte may be met with in the circulating blood. In this type of leukaemia the monocyte is said to be derived from the reticulo-endothelial system without any production of myeloid cells. If the existence of these two types of monocytic leukaemia be accepted, case 16512 approximates to the latter type i.e. leukaemic reticulo-endotheliosis whereas No. 264 is much less definite and approximates more nearly the first type.

In the light of the findings reported by previous observers, and of the appearances in the present case (16512), it may be stated that in this disease there is a widespread hyperplasia of reticulum cells, including sinus endothelium, with differentiation to monocytes. The appearances in the chronic form are of great significance, suggesting that, given time, the hyperplastic reticulum cells may differentiate in other directions particularly to fibroblasts.

HISTIOSYNCYTIAL RETICULOSIS.

This condition has been fully described by Dustin & Weil (1936). No example has been observed in the present investigation. The disease is characterised clinically by the usual features of an acute reticulosis and runs a very rapid course. Histologically/

Histologically there is a systematic hyperplasia of the reticulo-endothelial system throughout the spleen, where the pulp is especially affected, the bone marrow and the lymphatic glands. The liver shows infiltration with the hyperplastic cells, but the Kupffer cells are not involved in the hyperplasia. The hyperplastic tissue is composed chiefly of reticulum cells, but the characteristic feature is the presence of large multinucleated masses, sometimes with as many as 30 or 40 nuclei. The individual nuclei usually present a nucleolus. Dustin and Weil are of the opinion that the syncytial masses are formed by coalescence of reticulum cells. Some of the masses are not so large and resemble megakaryocytes. A small number of typical Dorothy Reed cells may also be present.

Although described as histiosyncytial reticulosis, the cells are not actively phagocytic, and Dustin & Weil regard the condition as a form of acute reticulosis.

Histiocytic Medullary Reticulosis is described as a separate entity by Robb-Smith (1938) and apparently similar cases have been described by other authors (Scott and Robb Smith 1939), (Asher 1946). The condition which presents the clinical features common to any of the reticuloses is relatively acute though the duration may be many months. According to Robb-Smith the characteristic histological features are hyperplasia of the reticulum cells particularly of the medullary portions of the lymphatic glands, associated with active phagocytosis

on/

on the part of the 'histiocytes'. Giant cells are also described , 'rather like pale-nucleated Sternberg cells'. Robb-Smith also describes numerous large non-phagocytic cells with single or multiple basophilic nuclei, which he calls pro-histiocytes. Similar cells have been frequently met with in the present study in many varying conditions but particularly in certain forms of sinus catarrh (Figs.7 & 8) and in the somewhat similar pictures met with in L. monocytogenes infection in rabbits. In the latter condition, although these cells were present along with many frank phagocytes, they were entirely different in appearance and none could be distinctly observed in the process of changing to typical macrophages. No example of histiocytic medullary reticulosis was recognised in the present study.

Giant-cell Histiocytic Reticulosis, is also described by Robb-Smith (1938) but even he appears to be doubtful as to its existence as a distinct entity, and considers that it may be identical with or at least, closely allied to sarcoidosis.

Comment on the Acute Reticulosis.

To sum up:- Case 101/39 represents an acute reticulosis with little or no differentiation.

19/46 represents an acute reticulosis with differentiation to macrophages and to a slight extent to fibroblasts.

125. represents an acute reticulosis with some differentiation to macrophages and slight production of monocytes.

264. represents an acute reticulosis with some differentiation to monocytes, and

16512 represents an acute reticulosis with great differentiation to monocytes, (monocytic leukaemia).

The differentiation between aleukaemic and leukaemic varieties of these conditions while convenient for purposes of study, appears to be of little significance as regards the course of the disease. It is difficult to say from the study of the peripheral blood, what the histological picture will be. Even in the present small series although cases 16512 and 264 both presented an increase of monocytes in the blood stream suggesting a diagnosis of monocytic leukaemia, the histological pictures were dissimilar, the only point in common being a hyperplasia of reticulum cells. This was much more intense in 16512 in which it was associated with a much greater increase in peripheral monocytes.

The distinction between an acute reticulosis and a malignant process may be very difficult. Acute reticulosis represents essentially a systematic involvement of a scattered series of cells, v.i.z. the reticulum cells, unlike the malignant processes which tend to begin locally. The acute reticulosis does not show the true invasive character of malignancy, and although in case 101/39 there was extensive involvement of the suprarenals, it was not clear whether this was a true invasion or whether the invasive cells had arisen from reticulo-endothelial elements present in the suprarenal. True metastases do not occur in the acute reticuloses, though there/

there may be some infiltration of the liver and other organs. The appearances in the present cases suggest that this infiltration occurs by the blood stream. The acute reticuloses are therefore to be regarded as systematic involvement of reticulum cells. In general these processes run such an acute course that there is but little time for local invasion to occur. Nevertheless in some instances the duration has been of several months. A time sufficient for the histopathological picture to become fully developed, and criteria typical of malignancy have not been present.

## CHRONIC RETICULOSES.

### DEFINITION.

Conditions characterised by an overgrowth of reticulum cells of lesser degree and slower progress than that met with in the acute reticuloses, and associated with more or less differentiation of the hyperplastic cells.

### EXAMPLES.

A. giant follicular hyperplasia.

This is a condition of some rarity. It is characterised clinically by chronic glandular enlargement, splenomegaly and finally irregular fever and anaemia. The course is chronic.

In the present series only one case was met with. (No. 1752/45 1950/43.) The disease first manifested itself towards the end of 1942 with enlargement of the left axillary glands, the enlargement was slowly progressive and biopsy was performed in November, 1943. Between November, 1943, and December, 1945, there was little change in the general condition of the patient but in the latter month enlargement of the left axillary glands became troublesome and was associated with considerable pain. An enlarged gland adherent to the axillary vein was removed. The pain was relieved, and there was satisfactory healing of the wound. In April, 1946, i.e., 3½ years from the time that glandular enlargement was first noted, further enlargement of the left axillary glands occurred, and there was rapid deterioration in/

in the general health. There was now a large mass of glands in the left axilla, the other superficial glands were slightly enlarged, and the tip of the spleen was palpable. A further gland was removed from the left axilla. The blood count at this time was not abnormal, apart from very slight anaemia. The general condition was however poor, and there was slight irregular fever. Death occurred on 1st May, 1946, and permission for autopsy was not obtained.

The histological appearances of the glands removed at the different phases of the disease are as follows:-

Nov. 1943. Fig. 60 the follicles were large, numerous and well defined. The central portions were composed of cells rather larger than those at the periphery, and much more loosely arranged. They were generally of rather angular outline, and were regarded as hyperplastic reticulum cells. The cells at the periphery of the follicles, and those of the interfollicular stroma and of the medullary cords were typical small lymphocytes. Mitotic figures were very scanty among the reticulum cells. The appearances were in general those of follicular hyperplasia of moderate degree. Sinus catarrh was not present, and in this respect this type of follicular hyperplasia was unlike that following irritation.

Dec. 1945. Fig. 61-63. the appearances were still suggestive of follicular hyperplasia, but the follicles were now much larger and more numerous. The central pale areas were/

were composed mainly of large cells of reticulum type, with moderately copious protoplasm. The nuclei were large with the chromatin arranged in fine strands and with a distinct nuclear rim. The cells however were much less uniform in size than in the previous specimen, and mitotic figures were more numerous. The whole appearance being suggestive of greater activity. Argyrophil reticulin fibrils were absent from the centres of the follicles, but were fairly numerous though fine among the peripheral cells.

April, 1946, Figs. 64 and 65. The histological picture had completely changed. The normal architecture of the gland had disappeared, and the whole structure was overrun by large cells with relatively large nuclei, rich in chromatin. In general the cell outlines were distinct though in some areas they tended to be arranged in syncytial sheets. Argyrophil reticulin was irregular and occurred mainly in coarse bands dividing the cellular tissue into trabeculae. Mitotic figures were numerous and the appearance in general was that of very rapid cellular multiplication. The cells were spreading through the capsule of the gland into the surrounding tissue.

COMMENT.

The case is significant in that for a period of over three years the process was apparently one of giant follicular hyperplasia of slow progress and relatively benign.

AT/

At the end of that time it underwent a blastomatous change assuming invasive characters; in short became sarcomatous. The appearances in December, 1945, although still suggestive of giant follicular hyperplasia were also suggestive of very rapid growth and resemble those seen in one form of lymphoblastic sarcoma described by (Gery & Bablet 1935).

B. CHRONIC RETICULOSES WITH DIFFERENTIATION.

INTRODUCTION.

This group comprises a great variety of conditions. The basic lesion is an overgrowth of reticulum cells. The hyperplasia however does not reach the extent seen in the acute types, and there is time for differentiation to occur. The process of differentiation goes on at the same time as the hyperplasia, and the resulting picture may be extremely varied, depending not only on whether hyperplasia or differentiation predominates, but also on the direction of differentiation. Thus the tissue may be comparatively cellular, or at the other extreme, almost completely fibrous. In the same case one lymph gland may show cellular hyperplasia, while another may be fibrosed. For this reason it is important when excising a gland for biopsy to remove a small one, in order to obtain a picture of the early stages which may still be cellular. In this group although, within limits, almost infinite variety is possible, certain histological pictures have been most frequently recognised. The most characteristic/

characteristic is represented by lymphadenoma, where reticulum cell hyperplasia is associated with many or even all of the possible lines of differentiation. The unrestricted differentiation described by Ross (1933), Pullinger (1932), refers to lymphadenoma as fibromyeloid reticulosis. If differentiation is predominantly in the direction of fibril production, the picture is that of fibrillary Reticulosis (Ross, 1933); (Tschistowitsch & Bykowa 1928). Should giant cell formation predominate, the result is the so-called giant cell reticulosis as described by Kettle (Case 4). If giant cell and fibril formation are both prominent features, but if there is no great pleomorphism, some authors, (Schulz, Wermbter & Puhl 1927); (Robb Smith, 1938) distinguish a special giant cell and fibrillary type. It must be admitted that the distinction between these different types is arbitrary, and strictly is only possible after a complete post-mortem examination with study of the histology of many groups of glands as well as the other portions of the R.E.S. The observation of Doan and Wiseman (1934) and Osgood (1937) that even in the acute reticuloses some portions of the reticulo-endothelial system may present a histological picture closely resembling lymphadenoma is extremely significant.

Clinically, all these conditions present the same general picture, namely a chronic illness associated with glandular enlargement, splenomegaly, sometimes hepatomegaly, slowly progressive anaemia, and irregular fever. The so-called Pel. Ebstein/

Ebstein type of fever, however, does appear to be characteristic of classical lymphadenoma. All are of comparatively chronic character and the duration may be months or years.

In addition to the group characterised by overgrowth of reticulum cells with differentiation to giant cells and to fibril or actual fibre formation, reticulum cell proliferation may be associated with over production of lymphocytes monocytes or even cells of the myeloid series (other sections).

EXAMPLES OF CHRONIC RETICULOSES WITH DIFFERENTIATION.

No. 308/37 (Figs. 66-69) was a case of glandular enlargement of six years' duration. In the lymphatic glands there were a considerable number of fine eosinophil interlacing fibres. Reticulum cells were numerous, and some of large size were lying free in spaces among the fibrils. The single nucleus of these cells was of the pale type met with in reticulum cells. Multinuclear giant cells were not present. Argyrophil reticulin fibrils were numerous. They were fine and were arranged to form a delicate meshwork. In the Malpighian bodies of the spleen there were mainly lymphocytes, but large reticulum cells were fairly numerous. There was considerable fibrosis of the splenic pulp which rendered the sinuses prominent. The sinus endothelial cells were swollen. The spleen indeed showed a combination of fibrosis with considerable cellularity. Argyrophil reticulin fibres were numerous throughout the spleen, both in the malpighian bodies and the pulp. The histological picture is interpreted as a reticulosis/

reticulosis of chronic type with differentiation to fibril formation. Although the disease was of long duration, fibrosis was not very advanced as was shown by the large amount of reticulin still present and the absence of much collagen.

In case 103/39 (Figs. 70-73) the duration of the disease was fifteen months. Histologically the lymphatic glands showed areas of considerable cellularity and other areas which were comparatively acellular. Giant cells were fairly numerous, many being of the type of large reticulum cells but a number were of the typical Dorothy Reed or lymphadenoma giant cell appearance. Fibrillary differentiation was evident but was not very advanced. The reticulum cells appeared to have differentiated to the stage at which they were producing argyrophil reticulin rather than collagenous fibres. Though the tissue was not especially cellular there was widespread involvement of the reticulo-endothelial system. In whatever situation the tissue was examined it presented the same characteristics i.e., a moderate degree of fibrillary differentiation was to be seen.

In case 108/39 (Figs. 74 and 75), although a much more acute example of only five months recognised duration, there was also a considerable degree of fibrillary differentiation. Reticulin fibrils were copious and coarse and there was also some collagen formation. Giant cells were rather scanty and there was no obvious accumulation of myeloid cells. In this case also the type of tissue was similar throughout those portions/

portions of the reticulo-endothelial system examined. A considerable degree of fibrillary differentiation had occurred in a relatively short period of time in this case.

Case 446/37 (Figs. 76-83), was of seven months duration and ran a relative acute course. The patient received a course of six exposures to deep X rays during the month before death. The typical tissue was of moderate cellularity and there were considerable numbers of giant cells. The basic tissue was however rather fibrous, argyrophil reticulin was prominent and the main tendency was for the reticulum cells to mature to fibrocytes. This tendency had been enhanced by exposure to X rays over a period of six weeks. The formation of argyrophil fibrils, which is generally a stage in the process of maturation of reticulum cells to fibrocytes appeared to have been completed and the case is therefore regarded as a reticulosis in which the process of fibrillary differentiation had been artificially expedited by exposure to X rays.

No. 169/39 (Figs. 84-87), this case was of one year's duration. Although the course was at first relatively chronic, during the last two months deterioration was rapid, and there was irregular pyrexia up to 102 F. with rapidly increasing anaemia.

HISTOLOGY.

Lymphatic Glands. The greater part of the glandular tissue was converted to a fibrillary tissue. A small gland still showed cellular areas in which reticulum cells were numerous. Some of/

of these cells were very large, and still presented a nucleus of the reticulum cell type with prominent nucleolus. Argyrophil reticulin was fairly copious in the cellular areas, and very copious in the fibrillary areas.

Spleen. Many of the Malpighian bodies were occupied by a fibrillary tissue similar to that seen in the glands. Towards their periphery large cells of reticulum type were numerous, some fixed and some free. Their nucleus was of the reticulum cell type.

In case 15950 (Figs. 88-94) the duration was just over three years. Until five months before death the progress was slow, but rapid deterioration occurred during the last five months. During the last six weeks which were spent in hospital, the disease ran a very acute course with pyrexia up to 102°F. A few exposures to deep X rays were given shortly before death.

Histologically the picture was one of a reticulosis with considerable fibrillary differentiation. In the more cellular, i.e. less differentiated areas, argyrophil fibrils were copious, whereas in the less cellular i.e. more differentiated areas they were scanty. In the latter areas the fibres had become collagenous and had ceased to take up the silver stain. In the splenic pulp there was considerable erythrophagocytosis, and there was swelling of the sinus endothelium. In this case, although histologically there was considerable differentiation, the disease ran a fairly acute course and the tissue, particularly/

particularly in the mediastinum, showed a certain invasiveness despite the fact that it was not particularly cellular.

Case 944/36 (Figs. 95 and 96), presented a different picture of reticulum cell hyperplasia. Giant cells were very numerous, many with only a single nucleus and resembling overgrown reticulum cells, but also many with multiple nuclei. Argyrophil reticulin fibrils were copious and gave the tissue a honeycomb appearance. This case might be described as an example of giant cell and fibrillary reticulosis. There was no obvious infiltration with cells of the myeloid series.

In No. 1242/39 (Figs. 97 and 98), a feature was the overgrowth of the lymphatic sinus lining cells of which some were becoming free in the sinuses. There was therefore hyperplasia of the reticulum cells, and sinus endothelial cells, with some giant cell formation and slight fibril formation. The large cells were mainly mononuclear, and the general picture resembled to some extent 16512 (monocytic leukaemia).

No. 34/37 (Figs. 99 and 100) resembled 1242/39 in that there was hyperplasia of sinus endothelium as well as of the general reticulum. There was however no true giant cell formation, though large cells of reticulum type with a single nucleus were numerous. No myeloid cells were to be seen, but reticulin fibrils were copious. In 1242 and 34/37 inasmuch as the sinus endothelial cells were involved in the hyperplastic process,/

process, and were in some areas becoming free in the sinuses, and the large cells were not typical Hodgkin cells, but rather large reticulum cells, the condition resembled that seen in monocytic leukaemia. On the other hand recognizable monocytes were not present among the hyperplastic reticulum cells or in the blood vessels of the gland. The tendency to giant cell production and the excessive development of reticulin fibrils pointed however to the Hodgkin group. It is possible that these two cases represent a link between monocytic leukaemia and lymphadenoma, both of which are essentially reticuloses, but with differentiation into different directions.

Case 477/37 (Figs. 101-106) was characterised by hyperplasia of the reticulum cells, among the lymphocytes of the glands. In some places the lymphocytes were still arranged in follicles. There were many large free cells with comparatively pale nuclei often with a nucleolus. These cells were 'distinct' from the reticulum cells. The endothelial cells of the lymph sinuses were swollen, and a few actively phagocytic large cells were present in the sinuses. In the spleen the Malpighian bodies were indistinct and small, and less cellular than normal. They presented a basis of fine pinkish fibrils which merged with a similar fibrillary arrangement throughout the pulp. In the meshes of this network, in the Malpighian bodies, there were some lymphocytes and reticulum cells. The sinuses of the pulp were outlined by/

by fine fibrils. The pulp contained very little blood. Reticulum cells were prominent among these fine fibrils. There was also swelling of the sinus endothelial cells. Very little erythrophagocytosis could be detected. In some areas of the splenic pulp there was localised fibrosis, not of dense type. Silver impregnation revealed a fine reticulin network throughout the lymph gland, and the spleen, both in the malpighian bodies and the pulp. In the splenic pulp the amount of reticulin varied from place to place. In the liver and kidneys there was extensive infiltration with cells, some resembling lymphocytes, but many much larger, and with oval or round nucleus. In some the nucleus was comparatively dark, in others it was of lighter texture, and more reminiscent of the nucleus of the reticulum cell.

The appearances in this case pointed to a hyperplasia of reticulum cells, and sinus endothelial cells throughout the lymph glands and spleen. There had been a production of a moderate number of large free cells, resembling monocytes. In addition there was considerable fibril formation. The case thus presents features reminiscent of monocytic leukaemia and features reminiscent of a fibrillary reticulosis. There was also extensive infiltration of the liver and kidneys.

In case 16002 (Figs. 107-109) there were unusual features. The duration of the disease was approximately one year. The blood picture showed a considerable increase of eosinophils, combined with an increase in large mononuclears.

Histologically/

Histologically the lymphatic glands showed a coarse eosinophil groundwork of interlacing fibres. At the same time they were cellular, many of the cells having the characteristics of lymphocytes, but in addition there were numerous recognisable reticulum cells and large numbers of free cells, particularly in the lymph sinuses, which were larger than lymphocytes, but smaller than reticulum cells. These cells were rounded or oval, with a simple rounded nucleus and often a nucleolus. There were also considerable number of macrophages free in the lymphatic sinuses. A few eosinophil leucocytes were scattered among the other cells. Argyrophil reticulin varied in amount in different parts of the same gland, and was not characteristic. In the spleen the Malpighian bodies were indistinct and consisted of a few lymphocytes, a few reticulum cells and fairly numerous large round cells of the type met with in the glands. The endothelial cells of the sinuses were swollen. The liver contained numerous nodules composed of a fine eosinophil fibrillary groundwork, with lymphocytes, reticulum cells and numerous free round type cells. In the nodules the liver cells had been destroyed, but bile ducts were present as in some cases of multilobular cirrhosis.

In certain respects this case was regarded as a reticulosis of moderately chronic type. It showed some resemblance to 264/45, though there was much more fibrillary differentiation/

differentiation, there was a somewhat similar production of large free mononuclear cells, with only a moderate hyperplasia of reticulum cells. The fibrillary differentiation coupled with the more chronic course, however, linked the case to the Hodgkin group, though the final picture was by no means typical of the true fibro-myeloid type of reticulosis, chiefly because of the absence of multinucleated giant cells.

The tissue was moderately invasive in character, and the exact classification of the case is not easy. On the appearances in a cervical gland removed several months before death, a tentative diagnosis of lymphatic leukaemia was considered, but was not supported by the haematological findings. At one time before the potentialities of the reticulum cell were understood, the case would probably have been classified as aleukaemic lymphatic leukaemia, or possibly as Hodgkin's Disease of malignant type. It was considered however that it should be regarded as a chronic reticulosis with fibrillary differentiation, and with a tendency to produce monocytes.

No. 308/34 (Figs. 110-112) represented an early stage of reticulum celled hyperplasia. Many lymphoid follicles were still present, and giant cell and reticulin fibril formation were very slight, i.e. very little differentiation had occurred.

No. 1319 (Fig.113) was also a relatively early example with a number of cortical follicles still persisting. The predominant/

predominant cell was the reticulum cell with typical vesicular nucleus and a single nucleolus. Some of these cells were extremely large. Reticulin fibrils were scanty.

In No. 2005/38 (Fig. 114 and 115) the normal follicular structure of the gland persisted to some extent. The hyperplastic reticulum cells were invading the follicles, and replacing the lymphocytes. Reticulin fibrils were increased among the reticulum cell, but absent among the lymphocytes. Although the process was at an early stage, there was considerable fibril formation by the reticulum cells, suggesting that differentiaition may occur at an early stage of hyperplasia.

These four examples illustrate a comparatively early stage of hyperplastic of reticulum cells. Some of these cells though very large, retained a single vesicular type of nucleus with nucleolus. A small number of multinucleate giant cells was being formed apparently by nuclear division from the reticulum cells even in these early stages the endothelial cells of the lymph sinuses were involved in the hyperplasia. Only in 2005/38 was differentiation to fibrils a feature.

No. 6/10 (Figs. 116 and 117) was a reticulosis with differentiation to fibril and giant cell formation, and in addition the gland was overrun with cells of the myeloid series. These cells were scattered throughout the substance of the gland, but were not to be seen in the blood vessels of the capsule. Their protoplasm was strongly eosenophilic, but their/

their nucleus was frequently simple.

No. 196/38 (Figs. 118 and 119) is regarded as a typical example of fibromyeloid reticuloses or Hodgkins Disease. Great hyperplasia of reticulum cells was associated with the presence of numerous giant cells, and with copious reticulin fibrils. Eosinophil leucocytes were numerous throughout the tissue. Some of the giant cells resembled closely megakaryocytes and it was difficult to escape the conclusion that myeloid cells were being formed in the gland.

In No. 1713 (Figs. 120 and 121) also there were numerous eosinophilic leucocytes again widely scattered throughout the tissue of the gland. Many of them had simple round nuclei. There was a considerable production of multinucleate giant cells, and argyrophil reticulin was increased.

These three cases are regarded as true fibro-myeloid reticuloses. There is considerable difference of opinion as to the origin of the eosenophil leucocytes in lymphadenoma. They are by no means invariably present in the chronic reticuloses, and even in that type referred to as fibro-myeloid or Hodgkin's Disease, they are not necessarily present. Pullinger (1932) found that in many of her cases of lymphadenoma, where eosenophil cells were present, the nucleus was of simple round type. It is her opinion that these cells are locally produced. The manner in which they are scattered throughout/

throughout the gland not in relation to the blood vessels, and their absence from the lumen of the vessels, lends support to this view, though it must be admitted that in the present investigation it has not been possible to observe the stages of their production in the glands.

## CHRONIC RETICULOSES WITH PRODUCTION OF LYMPHOCYTES.(LYMPHATIC LEUKAEMIA.)

In typical cases of lymphatic leukaemia, there may be considerable variation in the histological picture presented by the reticulo-endothelial system, but the predominant feature is an over-running of the tissue with lymphocytes. The normal architecture of the lymphatic glands is obscured by these cells. The Malpighian bodies of the spleen are also enlarged and composed of small lymphocytes. The picture then is one of fairly uniform cellularity but the lymphocytes are more loosely arranged, rather less uniform in appearance, and the framework of the gland is less distorted than in lymphosarcoma, also there is not the same tendency for the lymphocytes to infiltrate and pass through the capsule of the gland. In lymphatic leukaemia also,there tends to be more or less hyperplasia of the reticulum cells. In some cases this may be striking. The sinus endothelial cells may also be hyperplastic and erythrophagocytosis is often a prominent feature in the sinuses.

No. 176/37 (fig.122) was regarded as a typical example of lymphoid reticuloses of leukaemic type. The maximum leucoctye count was 148,800/cmm. of which almost 100% were small lymphocytes. Clinically a striking feature was/

was the profound degree of anaemia. Histologically there was comparatively little hyperplasmia of reticulum cells throughout the reticulo-endothelial system. Erythrophagocytosis was not a feature. The bone marrow however consisted almost entirely of small lymphocytes.

No. 55/37 (Fig. 123 & 124) was also a fairly typical clinical example of lymphatic leukaemia. The patient, a man aged 58 years died suddenly from coronary occlusion. The histological picture resembled 176/37, but there was rather more hyperplasia of reticulum cells, and macrophages were present in the sinuses and were actively erythrophagocytic. The lymphatic sinus endothelium was also swollen.

In such cases of typical lymphatic leukaemia the uniform cellularity consisting of what appear to be typical small lymphocytes is striking, especially in association with similar cells in the peripheral blood, In the blood and in the tissues, it has been impossible, in such cases, to distinguish the precursors of these lymphocytes or to detect with certainty any intermediate stage between the reticulum cell and the lymphocyte. Further, there may be large numbers of lymphocytes in the peripheral blood, as in 176/37 with only relatively scanty reticulum cells apparent throughout the reticulo-/

reticulo-endothelial system and it is difficult to see how the enormous numbers of lymphocytes in the blood and tissues could arise from these scanty reticulum cells, particularly as evidence of active proliferation of the reticulum cells such as mitoses are not obvious. It is indeed noteworthy that in lymphoid reticulosis mitotic figures are scanty even among the lymphocytes. It is difficult to escape the conclusion that the lymphocytes in such numbers are being produced by proliferation of a lymphocytic cell. From present observations it cannot be stated what this type of cell is, but in certain cases of chronic lymphatic leukaemia with large numbers of small lymphocytes in the peripheral blood, it may be impossible to detect any so-called lymphoblasts in the peripheral blood.

COMMENT ON THE IDEOPATHIC HYPERPLASTIC RETICULOSES.

These processes may involve the whole scattered system of reticulo-endothelial cells though the changes may be more striking in a particular portion of the system. The group corresponds generally to the true reticuloses and sinus reticuloses of Ross (1933) or the hyperplastic histiocytomatoses, with little tendency to malignancy of Epstein (1925). Leaving aside for the present frank examples of/

of myeloid and lymphatic leukaemia, the group centres on these processes involving proliferation of the reticulum cells. Formerly the group comprised a heterogeneous collection of diseases frequently classed as Hodgkins disease or atypical Hodgkins disease, or sometimes as aleukaemic leukaemia. At present with more exact knowledge of the classification of these conditions, there is a tendency to distinguish a considerable number of separate processes in the group, depending upon the predominant line of differentiation taken by the reticulum cell. Thus reticulum cell type, without differentiation ( Oberling & Guerin 1934). Giant cell type (Kettle case 4) Fibrillary type (Ross 1933 Casee 11.) Giant cell and fibrillary type (Schulz, Wermbter & Puhl 1927). Prohistiocytic type (Robb Smith 1938). Histiocytic type (Pullinger 1932) Histiosyncytial type (Dustin & Weil 1936). Monocytic type, and finally unrestricted differentiation or lymphadenoma. This subdivision of the group serves a useful purpose in the present state of ignorance as to aetiological factors. It enables an exact histopathological classification to be applied to any such process, and it is of use clinically as the prognosis varies to some extent with the type and the degree/

degree of differentiation of the hyperplastic cells. It is most important however that the basic similarity of the processes should be appreciated.

Clinically the group is sharply divided into acute and chronic types, though a case which has run a chronic course may at any time suddenly become acute, e.g. 15950. Histologically the appearances may vary even in the acute types, thus there may be a pure hyperplasia of reticulum cells as in 101/39 or a great development of macrophages as in 19/46, or of monocytes, as in 16512.

In all, however, the fundamental process is hyperplasia of the reticulum cell. The variability of the histological appearance is even more striking in the chronic cases. Giant follicular hyperplasia appears to constitute a distinct picture, though even here the process is essentially one of reticulum cell hyperplasia confined largely, but not entirely, to the follicular reticulum cells. The other chronic reticuloses are all similar to one another and vary merely in the predominant line of differentiation, and the stage of differentiation reached at the time of examination. The tendency appears to be for the processes to become fibrotic if the duration is sufficiently long. Necrosis and caseation rarely, if ever, occur.

Certain/

Certain of the processes may be associated with qualitative or quantitative changes in the circulating leucocytes, and opinions vary as to whether a distinction should be drawn between the aleukaemic and leukaemic forms. Oberling & Guerin (1934) consider that such a distinction is open to criticism. They take the view that the hyperplastic reticulum cell, being multipotential, may give rise to cells of the myeloid, lymphoid or monocytic type, and that they may be produced in different proportions at varying stages of the same disease. They explain thus these apparent examples of monocytic leukaemia in which a sudden outpouring of myeloid cells may occur. Nevertheless, even they regard myeloid and lymphatic leukaemia as distinct and well-defined entities, and admit that it may on occasion, though rarely, be justifiable to use the term monocytic leukaemia. In the present work the only true example of monocytic leukaemia was acute, and is classed with the acute reticuloses. Remembering that a chronic form of monocytic leukaemia, in which the histological changes resemble those met with in Hodgkins disease, i.e. fibroblastic differentiation, has been described, the histological changes in that disease may be summarised as hyperplasia of reticulum cells with monocytic/

differentiation if acute, proceeding to fibroblastic if chronic. It is therefore debatable whether the condition should be classified as a leukaemia or whether it is more justifiable to regard it as a reticulosis with tendency to produce monocytes. Compared with the other two common leukaemias, it presents important differences. In lymphatic leukaemia where the reticulo-endothelial system may be overrun with lymphocytes, it has not been possible to demonstrate conclusively the development of the type cell from the reticulum cell. Though there may be some hyperplasia of reticulum cells, it is disproportionately small compared with the enormous number of lymphocytes which may be present, also mitotic figures are very scanty. The impression obtained in the course of the present study is that the lymphocytes are derived from other cells of the same type, and that production is not thrown back as far as the reticulum cell. This view is also held regarding myeloid leukaemia, and it is considered, that lymphatic and myeloid leukaemia constitute distinct entities involving hyperplasia of already differentiated cells, and that they cannot strictly be regarded as reticuloses except in so far as the myeloid and lymphatic series are originally derived from/

from the reticulum cell, or from a closely related mesenchymal element. The results of the present investigation support the view that the origin of the monocyte is distinct from that of the myeloid and lymphatic series, and that the cell is more closely related to the reticulum cell.

# NEOPLASTIC RETICULOSIS.

## Introduction.

Malignant hyperplasia may involve the multipotential reticulum cell or any of its offspring. The malignant processes affecting the differentiated and defined derivatives are well-understood and classified. Indeed when malignant hyperplasia involves a cell type which is well-defined, it cannot strictly be regarded as an example of neoplastic reticulosis. This is true of the myeloma, plasmocytoma, erythroblastoma and possibly of the lymphosarcoma. On the other hand when malignant hyperplasia affects the undifferentiated reticulum cell, a certain degree of cellular differentiation may go on coincidentally with the hyperplastic process. Thus the most primitive type of tumour growth affecting the reticulo-endothelial system is the reticulum celled sarcoma, and the more rapid the cellular multiplication, the less is the differentiation, just as in the ideopathic reticulosis.

## Classification:

The recognition of malignant hyperplasic affections of the reticulo-endothelial system is fairly easy, but the detailed classification of the process is generally extremely difficult. Various classifications have been suggested and/

and that proposed by Gery and Bablet (1935) provides a useful basis .

The classification of tumours of the lymphoid tissue suggested by these workers includes the malignant processes affecting the reticulum cell. Three main subdivisions are recognized viz.

1. Reticulosarcoma.
2. Dictyocytic sarcoma.
3. Lymphoblastic Sarcoma.

Clinically all three types are characterised by a high degree of malignancy with very rapid formation of metastases which may appear early, at a considerable distance from the primary growth, so that it may even be difficult to decide which is the primary site, and the process may assume the appearance of a systematic disease of the reticulo-endothelial system. Local invasiveness is generally not great. All three types are extremely radio-sensitive, but the possibility of eradicating the whole process even temporarily is hopeless. Though changes in the blood picture are rare, elements of the tumours may escape into the blood stream and some part of the dissemination may occur in this way.

The distinction between some types of acute reticulosis and reticulum celled sarcoma may be very difficult/

difficult. Clinically the latter tend to run a slightly less acute course. They generally present themselves locally in one gland or group of glands whence the metastases arise, whereas the acute reticuloses affect the reticulo-endothelial system more or less completely from the outset. Histologically there are difference between the acute reticuloses and the reticulosarcomata.

RETICULOSARCOMATA.

Histologically these tumours are entirely undifferentiated and represent a malignant hyperplasia of the basic reticulum cells forming a syncytium. The cell outlines are therefore indistinct. The malignant tissue may undergo some degree of evolution constituting the so-called reticulo-endothelio sarcoma.

Differentiation may also occur into one or other of the cellular forms viz:

Dictyocytic sarcoma in which the cell outlines are distinct and there is a tendency for the cells to be connected to one another by fine protoplasmic processes. Differentiation to the dictyocytic stage may be confined to one area, for example of a lymphatic gland, the remainder of which presents the appearance of the primitive syncytial reticulosarcoma. Reticulin fibrils may be formed in considerable/

considerable amount. Several types of dictyocytic sarcomata are described, and this type of malignant process may show great variations in its histology. In one type the cells are uniform in size and shape, in another they vary greatly in size and giant forms may occur, in which case the picture closely resembles that of so-called malignant Hodgkin's disease. The second cellular form is that in which there is differentiation to the lymphocytic series. In this group the typical lymphocytic sarcoma is clearly defined. It is composed of uniform cells almost exactly resembling the small lymphocyte. This is the typical lymphosarcoma and is relatively common. Most workers however endeavour to distinguish at least one other subdivision in this lymphoid group. Robb-Smith (1938) refers to the lymphoblastic type which may affect chiefly either the lymphoid follicles or the medulla of the lymphatic glands. Gery and Bablet (1935) distinguish a lymphadenoid type in which the cells are much less uniform than in the lymphocytic type. The malignant cells tend to collect in foci giving to the lymph glands the appearance of hyperplastic follicles. According to these authors this type runs a much more chronic course than the lymphocytic variety and corresponds in great measure to so called malignant Hodgkin's Disease.

Gery/

Gery & Bablet consider that the demonstration of reticulin fibrils is by no means constant in tumours arising from the reticulo-endothelial system. In general, reticulin is more likely to be produced in the cellular types of tumour, and less so in the syncytial types. Some of the reticulin described in certain of the processes is probably the residue of the normal reticulin of the lymph gland.

The classification of these tumours may be thus summarised:

| | |
|---|---|
| 1. Reticulosarcoma. | Syncytial with no differentiation. |
| 2. (A) Reticuloepitheliosarcoma. | With areas of differentiation to epithelial-like elements. Most frequently met with in the thymus gland. |
| (B) Reticuloendothelio sarcoma. | With areas of differentiation to flat endothelial cells. A rare type. |
| 2. Dictyocytic sarcoma. | With separation of individual cells which often produce fibrils. |

(A) Typical lymphosarcoma.
(B) Lymphoblastic Sarcoma.
(C) Lymphadenoid. Hodgkin's Sarcoma.

Case 16184 (Figs. 125-130) is regarded as an example of reticulosarcoma, and presents certain unusual features. The duration of the disease was approximately six months, and the presenting signs were of a mediastinal tumour, being mainly pressure effects with moderate enlargement of the cervical glands. The presence of a mediastinal tumour was confirmed by X-ray examination, and the mass reacted rapidly to deep X-ray therapy. The enlargement of the cervical glands also greatly diminished, and the patient was discharged. On re-admission one month later, there was generalised enlargement of the superficial lymphatic glands and the liver and spleen were also enlarged. X-rays showed that the mediastinal mass was still small.

Post-mortem the mediastinal glands were greatly enlarged, and in the lower lobe of the right lung was a small tumour. Scattered over the peritoneum were numerous small cherry-like nodules. Arising from the lining of the small intestine were hundreds of spherical or oval, dark red tumours, some minute, some the size of a cherry. They were most numerous in the jejunum and on passing down the bowel became fewer and smaller. They ceased completely at the ileo-caecal valve. The retro-peritoneal glands were much enlarged/

enlarged. The right suprarenal was almost destroyed. In the liver were scattered numerous small red spherical tumours, and fleshy masses of similar type were present in the porta hepatis. A small tumour was present in the pericardium. Histologically the neoplastic tissue, in whatever situation it occurred, had the same characteristics. The tissue was very cellular and in the lymph glands the normal architecture was completely destroyed. They type cells were of moderate size, larger than lymphocytes, and tightly packed. The individual cell outlines were often indistinct giving a syncytial appearance. The nucleus had a distinct rim and the chromatin was arranged in a more delicate pattern than that commonly seen in cells of the lymphocytic series. The cells were divided into compartments by bands of coarse fibrous tissue. Argyrophil reticulin fibrils were very scanty. The appearance in this case were regarded as those of a malignant process, the predominant cell being of reticulum cell type. The case presents many interesting features. From the clinical point of view it was characterised initially, by a rapidly growing tumour of the mediastinum, which reacted favourably to deep X-rays, but very shortly was followed by general enlargement of the lymphatic glands, liver and spleen, and proved rapidly fatal. Post-mortem apart from the glandular enlargement, the/

the most striking feature was the enormous number of tumours in the small intestine.

The proliferative process was widespread throughout the reticulo-endothelial system. The pericardial foci were in relation to small blood vessels, and the spread throughout the liver was extremely diffuse, suggesting spread by the portal vein from the intestine. The multiplicity of the tumours in the small intestine, and the fact that they became smaller and less numerous on passing downwards, suggests that some spread may have occurred by direct seeding of detached cells. There was also evidence of spread by lymphatics, the cervial glands being enlarged from an early stage, while the disease was largely confined to the mediastinum. No.15923 (Figs. 131-135) illustrates a somewhat similar process. The duration was approximately five months. Early features were anaemia and moderate splenomegaly, and a tentative diagnosis of splenic anaemia was made. The patient was a diabetic. Thereafter the left supraclavicular and cervical glands became enlarged and X-ray examination revealed enlargement of the mediastinum. There was moderate anemia with leucopenia. Post-mortem in addition to the enlargement of the cervical glands these of the mediastinum were also enlarged, but the retroperitoneal group were much more affected and were matted together in

a/

a large tumour-like mass which extended to embrace the lower pole of the right kidney. Another tumour mass was present in the pouch of Douglas. The liver and spleen were enlarged especially the latter.

Histologically throughout the reticulo-endothelial system the same type of tissue was present.

The typical structure could be seen in the tumour mass from around the pole of the kidney. The tissue was extremely cellular. The cells were relatively large and uniform. The nucleus was large in proportion to the cell. Its texture was moderately light. The cell outlines were fairly distinct, though in places there was a tendency to syncytial formation. Mitotic figures were numerous. A few normal-looking basic reticulum cells could be seen. Thin-walled blood vessels were numerous. There was little, if any, new formation of reticulin. The bone marrow was completely occupied by similar cells which showed a tendency to orientate themselves around the fat spaces, which tendency was also noteworthy in the retroperitoneal tumour tissue, where the appearances suggested endothelial differentiation.

The liver presented fairly numerous small foci of infiltration with similar cells, and in addition there was/

was some diffuse scattering of the cells throughout the liver capillaries. In the spleen the Malpighian bodies were indistinct and the pulp was extremely cellular, the cells,which were of the type described,were present in the sinuses and in the intersinusoidal trabeculae. Mitotic figures were frequent. There was no infiltration of the kidneys.

These two cases illustrate a process of high malignancy, in both the known duration was about six months. Although at death there was widespread involvement of the reticulo-endothelial system, one area was obviously involved at an early stage; in the first case the mediastinal glands, and in the second retro-peritoneal para-aortic glands.

In No. 700 (Figs. 136 and 137) the normal architecture of the gland was destroyed. The structure consisted of cells somewhat larger than a lymphocyte, with a slightly lighter nucleus in which the chromatin was generally arranged in a number of small particles.

The cells outlines were not well defined. Their protoplasm which was neutrophil in staining reaction was drawn/

drawn out into a series of fine processes which united to form a reticular meshwork. In places the cells formed large protoplasmic sheets. A few typical basic reticulum cells with pale nucleus could be seen here and there incorporated in the syncytium. Mitotic figures were not numerous.

There were a few strands of coarse fibrous tissue in places. Erythrophagoctyosis was slight.

Reticulin varied from place to place but was not copious and appeared to represent mainly the residue of the normal reticulin. The cells were spreading through the capsule of the gland.

Case 782 (Figs 138 & 139) was of very similar character though large basic reticulum cells were more prominent and there were fewer fibrous strands Erythrophagocytosis was very slight and reticulin was not increased. In 778 (Figs. 140 & 141) there is some resemblance to the two previous examples, but large cells of reticulum type, some of giant proportions were a feature. There was also a fair quantity of fibrous tissue though it was of fine texture. There was little if any new formation of reticulin. In 800 (figs. 142 & 143) the arrangement was partly syncytial, but there were fairly numerous free cells and moderately large reticulum cells of normal type/

normal type were present. There was one increase in the number of reticulin fibrils.

CLASSIFICATION OF THE PRESENT EXAMPLES.

No. 16184 and No. 15923 are regarded as examples of reticulosarcoma with very little differentiation to dictyocytes, i.e., they are tumours of a very primitive type in which proliferation has predominated with little or no differentiation.

No. 1752 and 600/46 has been described above as an example of giant follicular hyperplasia which ran a relatively slow course, but after the lapse of three years the appearances of a lymph gland, while still suggesting giant follicular hyperplasia, could not be regarded any longer as typical of that condition. The cells of the paler central portions of the follicles were very variable in size. Their nuclei varied in staining reaction, and mitotic figures were numerous, the appearances in fact correspond to those of the lymphadenoid type of lymphoblastic sarcoma figured by Gery and Bablet (1935). Six months later however, the picture was very different, and suggested a malignant proliferation of a more primitive type of cell, and though in some places the cell outlines are distinct/

distinct, in others they have a syncytial arrangement, and it is felt justifiable to regard the final condition as reticulosarcoma.

Nos. 700, 782, 778, and 800 are regarded as varying type of dictyocytic sarcomata. No example of monocytoma has been encountered in the present study.

## PART III.

## EXPERIMENTAL LISTERALLA MONOCYTOGENES.

## INFECTION IN RABBITS.

### Introduction.

Since the Listerella Monocytogenes was first isolated from a naturally occurring epidemic in rabbits by Murray Webb & Swann (1926) it has been frequently employed in investigations into the origin of the monocyte. One of the earliest studies was made by Witts & Webb (1927), who after stimulating a considerable production of monocytes in a series of rabbits, studied the blood and tissues, using supravital staining with neutral red and Janus green, as well as fixed films stained by the Romanowsky dyes. They came to the conclusion that the monocytes produced after infection with L. monocytogenes, arose in the spleen and bone marrow but not in the lymph glands. They noted no change in lymphocyte production and no appearance of "Clasmatocytes" in the circulating blood. Further if the animal was stained intravitam with lithium carmine, trypan blue or india ink, before infection with L. monocytogenes, no dye or carbon particles appeared in the circulating monocytes. If the rabbit were first infected with L. monocytogenes and subsequently stained with india ink the monocytes failed to take/

take up the carbon.

W. Bloom (1928) carried out a similar series of experiments employing both supravital and dry smear preparations. He concluded, that (1) the monocytes develop in the circulation by individual transformation of lymphocytes in the blood, and states that there are always numerous mitoses in the lymphoid tissue to account for the new formation of lymphocytes (2) in none of the organs is there any evidence of the transformation of fixed cells (mesenchymal or histiocytes or vascular endothelium) into monocytes (3) if the newly formed monocytes, which are present in such numbers, were to arise diretly from any fixed or free cells, many mitoses should appear in the so-called parent cells to account for the numbers of new cells. These do not occur. (4) The monocytes should be sharply discriminated from free histiocytes, although they may develop into histiocytes in vitro or in vivo.

Conway (1938) concludes that the monocytes which are produced in great numbers in infection with L. monocytogenes arise from lymphocytes. She states that the initial response to the infection, in both the rabbit and the guinea pig, is a mobilisation of the lymphocytes present in/

in the lymphoid tissue followed by an intensive new formation of lymphocytes. During the height of the initial hyperplasia,which precedes the peak of the monocytosis in the peripheral blood, all stages of transition between lymphocytes and monocytes are found throughout the diffuse and nodular lymphatic tissue of both the mesenteric lymph node and the spleen. Conway further states that there is complete absence of cells other than lymphocytes transforming into monocytes. A criticism of these opinions is that, thought it is stated that the small lymphocytes in the peripheral blood stream rose from a pre-injection figure of 26 per cent to 48 per cent at 24 hours, it is also stated that the injection of L. monocytogenes was followed by leucopenia,and the absolute lymphocyte counts are not quoted. In the present investigations there was no absolute increase of lymphocytes in the peripheral blood after injection of L. monocytogenes. Witts and Webb (1927) also noted no change in the lymphocyte production. Many such investigations have been carried out, but it must be admitted that the exact development of the monocyte has never been definitely observed, though it is generally agreed that it is derived from the reticulo-endothelial system either directly or indirectly.

SCOPE OF THE PRESENT INVESTIGATION.

In the course of investigation on the blood monocytes, using the Listerella monocytogenes as a stimulator of monocyte production, it was observed that striking changes occurred throughout the reticulo-endothelial system of experimentally infected rabbits. In the present investigation the L. monocytogenes has been employed, not so much in an attempt to determine the origin of the blood monocyte, as to produce observable changes in the reticulo-endothelial system. It was noted that these changes resembled, in certain respects, some of the disease processes naturally affecting the reticul-endothelial system in man and in order to study these reactions more fully the present experiments were carried out.

MATERIAL AND METHODS.

If the L. monocytogenes be maintained in culture its potency rapidly diminishes, if however a rabbit be inoculated with a relatively large dose of this comparatively inactive organism, the bacterium may be readily recovered from the spleen, its potency being increased with each passage. In this way a potent culture was obtained. The effect/

effect of infection with such a culture is shown in Table 3. The results of two similar infections are shown in Tables 12 and 13. In the first case the infection was combined with intra-vitam staining of the animal with Trypan Blue, in the second, at the height of the monocytosis, india ink was injected. It will be noted that the monocytes were unstained by Trypan Blue and took up the ink to an almost negligible extent. Having obtained a potent culture, eight healthy young rabbits were selected and after examining the blood, each received into the marginal vein of the ear a relatively large but non-lethal dose of the L. monocytogenes suspended in physiological saline. The blood was then examined every twelve hours, and one rabbit was killed at the end of each twelve hour period up to 72 hours, and thereafter one at 120 hours, and one at 144 hours. Small portions of liver, spleen, bone marrow and mesenteric glands were fixed in Zenker's fluid. Sections were then stained as a routine with haemotoxylin and eosin. Eosin methylene blue was also used in some cases, and certain of the tissues were stained for iron. Reticulin impregnation was carried out by the Wilder-Foote technique. Blood films were stained as a routine by Leishman's stain.

RESULTS.

A satisfactory but not excessive increase of monocytes occurred in the circulation in each case, Tables 4-11.

In each case and although the investigation was not primarily concerned with the nature of the monocyte, those observed did not appear to differ in any important respect from those normally occurring in the blood. In those animals which were allowed to survive for several days polychromatophilic staining of the red corpuscles was noted and nucleated red cells were fairly numerous in the peripheral blood. These phenomena became apparent during the time that erythrophagocytosis was prominent in the reticulo-endothelial system. Those animals killed at an early stage of the infection, presented numerous small pale foci scattered throughout the liver and spleen. Histologically these foci were small abscesses.

HISTOLOGICAL CHANGES IN THE RETICULO-ENDOTHELIAL SYSTEM.

1. Lymphatic glands. At 12 hours (Fig.144) the afferent sinus contained only a few cells, chiefly lymphocytes. In the cortex the lymphocytes were arranged compactly but not in distinct follicles. In the medulla the arrangement was looser. Throughout both cortex and medulla the vast majority of the cells were small lymphocytes. Reticulum cells with their large pale nucleus and single nucleolus were relatively prominent in both cortex and medulla. The medullary sinuses contained few cells, mainly lymphocytes,/

lymphocytes, and the sinus endothelium was not swollen.

At 24 hours - The appearances were very similar but reticulum cells were more prominent in both cortex and medulla, and a few large phagocytic cells were present in the sinuses especially of the medulla.

At 36 hours (Figs. 145-147) - The reticulum cells were still more prominent. In the sinuses especially of the medulla, there were many large free mono-nuclear cells whose rather dark nucleus had usually a single nucleolus. The protoplasm was faintly basophilic. In addition there were a number of large phagocytic cells with faintly acidophil protoplasm and pale nucleus also with a single nucleolus. There was slight swelling in places of the medullary sinus endothelium. Erythrophagocytosis was observed, especially by the large eosinophil phagocytic cells, but to a slight extent also in the swollen sinus endothelium.

At 48 hours the appearance were similar, but the large phagocytic cells were present in greater numbers in the medullary sinuses.

At 60 (Figs. 148-149) hours, the histological changes reached their maximum. The cortical lymphoid follicles were distinct but not unduly large. The central portions of some

were/

were rather pale, and were composed of fairly large cells of reticulum type, some of which were elongated and angulated with rather copious faintly eosinophil protoplasm, but many were rounded in outline. Scattered through the substance of the cortex and the medullary cords, there were numerous reticulum cells frequently united to one another by fine protoplasmic processes. Also scattered in the same situations were less numerous large cells with a pale nucleus, single nucleolus and copious eosinophil protoplasm, which were frequently in the process of erythrophagocytosis. These cells in places coalesced to form large plaques. Also in the substance of the cortex and medulla there were numerous large rounded faintly basophil cells with a single relatively large, often indented nucleus showing a distinct nuclear rim, chromatin strands of moderate texture, and frequently a single nucleolus. A number of these cells were undergoing mitosis. No phagocytic activity was noted on the part of these cells. Both types of cell were present in large numbers in the sinuses particularly of the medulla, where the large acidophil phagocytes frequently formed a branching network traversing the sinus. Swelling of the actual lining endothelium was not a feature. At 72 (Figs 150 & 154) hours there was little basic change, though the central portions

of/

of the cortical follicles were paler, less cellular and in places looked almost fibrous. The number of acidophil phagocytes rounded and free in the medullary sinuses was greatly increased. Large basophil mononuclears were also numerous, especially in the substance of the medullary cords where they tended to be aggregated just deep to the sinus endothelium. The endothelial cells of the sinuses though readily discernable, were not much swollen, and were not erythrophagocytic, though the large free acidophil cells were. At 120 (Fig. 155) Hours the large acidophil phagocytic cells were less prominent, whereas the large basophil cells were still numerous, both in the substance of the gland and in the sinuses. The great majority of these cells had an indented nucleus relatively large compared to the size of the cell, and resembled blood monocytes. The sinus endothelium was prominent but not strikingly so.

At 144 (Figs. 156-158) Hours the cortical follicles were numerous and the general picture suggested follicular hyperplasia, though the central parts of the follicles were more fibroblastic in appearance.

The large type of acidophil phagocyte was still fairly prominent and was still ingesting erythrocytes. The large basophil cells were much less numerous.

SUMMARY OF APPEARANCES IN LYMPHATIC GLANDS.

The earliest changes were an increase in conspicuousness of the basic reticulum cells of the inter-follicullar cortex and the medulla, together with the appearance of large eosinophil phagocytes especially in the medullary sinuses. The basic reticulum cells rapidly became more conspicuous and large free basophil cells appeared both in the lumen of the medullary sinuses and in the solid tissue of the gland, especially of the trabeculae of the medulla. Soon large eosinophil erythrophagocytic cells appeared also in the solid tissue of the gland. The centres of the cortical follicles became paler and were composed of irregular reticulum cells. At the later stages these reticulum cells tended to become elongated and resembled fibroblasts. The eosinophil phagocytes were large and irregular, and were sometimes fixed forming a network in the sinuses or sometimes in the solid tissue of the gland. Sometimes they were rounded and free in the sinuses. Their nucleus closely resembled that of the reticulum cell being pale with a distinct rim, with a single nucleolus from which the chromatin radiated in delicate strands.

The large basophil cells were free and rounded with a relatively large nucleus. The nucleus was fairly dark/

dark with moderately coarse chromatin. In some cases the nucleus was rounded with a single nucleolus, in others it was indented and paler, in which case the cell resembled closely the large monocyte. The basophilic cells were frequently observed in mitosis. The ordinary lymphocytes of the gland did not present mitoses. Swelling of the true sinus endothelium was not a feature at any stage.

SPLEEN.

At 12 Hours (Fig. 159) the Malpighian bodies were well-defined and the germ centres were compact. The pulp was not particularly cellular and contained much blood, so that the sinuses were obscured. A few basic reticulum cells were present in the Malpighian bodies.

At 24 (Fig. 160) hours, the appearances were not much changed. The Malpighian bodies were still sharply demarcated from the pulp. Reticulum cells were rather more prominent in the Malpighian bodies and a few showed mitotic figures.

At 36 (Figs. 161-163) Hours the Malpighian bodies were still sharply demarcated. In almost every Malpighian body there was a small compact focus of eosinophil polymorphonuclears usually in relation to the small artery.

The/

The appearance was that of minute abscesses. Reticulum cells were rather more numerous.

At 48 hours the appearances showed little further change.

At 60 (Figs. 164-165) Hours the Malpighian bodies were less clearly demarcated from the pulp which was now more cellular, especially around the malpighian bodies. There was less blood in the sinuses of the pulp, and some erythrophagocytosis was occurring. Around the periphery of the Malpighian bodies there was a rim of large cells merging with the pulp. These cells were fairly compactly arranged, and were irregular in outline with neutrophil protoplasm. The nucleus was rather pale, with a well-defined rim and sometimes with a single nucleolus. The endothelial cells of the sinuses were swollen. A number of large free cells, with acidophil protoplasm and pale nucleus with usually a single nucleolus, were actively erythrophagocytic in the sinuses.

At 72 (Figs. 166-168) hours the cellularity around the Malpighian bodies was greater, the cells being of the type already described. Mitotic figures were numerous among these cells. In the Malpighian bodies the cells showed considerable pleomorphism. There were numerous large cells closely resembling those aggregated at the/

the periphery of the bodies, which also presented numerous mitoses. A number of typical lymphocytes were also present and in addition there were a few large acidophil phagocytic cells. The pulp was less vascular and much more cellular with considerable thickening of the intersinusoidal trabeculae. In the trabeculae the cells were largely of the type seen around the Malpighian bodies. The sinusoidal endothelial cells were swollen but not strikingly so. In the sinuses there were a number of large acidophil phagocytes and a small number of free rounded basophil cells with indented nucleus, closely resembling monocytes.

At 120 (Fig. 169) hours the appearances were similar, but less striking. There were numerous acidophil phagocytes in the Malpighian bodies, where they were frequently fused to form large plaques. Apart from these plaques, the cellularity of the Malpighian bodies was comparatively uniform, with few large basophil cells and very few mitotic figures. The pulp was still cellular with some swelling of the sinus endothelium and with a number of free acidophil phagocytes. A few of the basophil cells resembling monocytes were still present in the sinuses. The bulk of the cells in the pulp however, were the hyperplastic reticulum cells of the intersinusoidal trabeculae.

At/

At 144 (Fig. 170-176) hours there were still a number of recognizable reticulum cells among the lymphocytes of the Malpighian bodies, a few large acidophil plaques were also present. Mitoses were almost absent. The pulp was fleshy and comparatively avascular. The sinuses were small and their walls greatly thickened by proliferation of reticulum cells.

SUMMARY OF APPEARANCES IN THE SPLEEN.

The appearances in the spleen consisted of hyperplasia of the reticulum cells in the Malpighian bodies and in the pulp. Two distinct types of cell then became prominent. The first was the large irregular acidophil cell, with pale rounded nucleus, showing a distinct nuclear rim. A single nucleolus was generally present, and the chromatin was arranged in fine strands radiating from the nucleolus. This cell was actively phagocytic towards the red corpuscles, especially in the sinuses, but also to some extent in the Malpighian bodies, where it tended, in the later stages, to form large multinucleated plaques. The second type of cell was the large basophilic mononuclear. This cell was smaller than the large phagocyte, it was free, rounded and never phagocytic. The nucleus was relatively large, sometimes rounded, but more frequently indented when it closely resembled/

resembled the large mononuclear of the blood. These cells frequently showed mitotic figures. They made their appearance in the substance of the Malpighian bodies especially towards their periphery,at the junction of the red and the white pulp, but later they were scattered throughout the Malpighian body. They also were present in the intersinusoidal trabeculae, and in the sinuses. At a later stage (144 hours) the pulp of the spleen became fleshy, due to an increase of fixed reticulum cells, the appearance suggesting an early stage of intersinusoidal fibrosis. Swelling of the sinus endothelium was not a striking feature at any stage, though the cells were moderately prominent.

DISCUSSION OF THE HISTOLOGICAL APPEARANCES.

From these observations on the lymphatic glands and spleen, it appears that infection with Listerella Monocytogenes acts as a powerful stimulant to the reticulo-endothelial system and more especially to the reticulum cell. At an early stage the production of macrophages seemed to depend upon stimulation of the existing potential phagocytes,normally present in the lymph sinuses of the glands,and in the blood sinuses of the spleen. These cells,in the resting state, were relatively inconspicuous and were sometimes applied to the walls and sometimes formed a rather scanty network across/

across the lumen of the sinus. When stimulated these became larger and much more conspicuous, they might still form a network, or they might be free and rounded or of irregular outline. At a later stage similar cells became prominent in the solid tissue of the glands and spleen; in the medullary trabeculae and inter-follicular cortex of the glands, and even in the cortical follicles themselves. In the spleen they developed in the Malpighian bodies. In all those situations they sometimes formed plaques. They were actively phagocytic towards the red corpusdles. Their nuclear characteristics closely resembled those of the basic reticulum cell and the available evidence strongly suggested that they were derived from the reticulum cell.

It is noteworthy that even with considerable stimulation and the production of large numbers of marcophages, swelling of the sinus endothelium was not a notable feature.

LARGE BASOPHIL CELLS.

These cells constituted a striking picture, and were very numerous. The present investigation is not primarily concerned with their exact nature, but certain of them closely resembled large monocytes, while others approximated more to the reticulum cell in appearance. They resembled the type of cell frequently met with in the acute reticulosis/

reticulosis, and very similar cells were described by Dustin & Weil (1936) in their case of acute histiosyncytial reticulosis. It is considered that they were free stimulated reticulum cells (or histiocytes). As is the rule with this type of cell they were not erythrophagocytic. They showed numerous mitoses. As stated above a proportion of them closely resembled monocytes and it is difficult to escape the conclusion that they were in fact identical with the monocytes which appeared in increased numbers in the peripheral blood. In the present investigation the lymphocytes did not present mitoses. Another possibility is that the large basophilic cells, resembling the reticulum cell, were in reality haemocytoblasts, either rendered more apparent or derived from the reticulum cells under the stimulating influence of the L. Monocytogenes and that from them the monocytes were derived. This however is speculation, but it does appear probable that the monocyte produced in response to the L. Monocytogenes is derived mainly, if not entirely, from the reticulum cell of the lymphoid tissue of the spleen and the lymphatic glands, either by a process of maturation or indirectly through a precursor (? the Haemocytoblast) and not by a process of modification from the lymphocyte. This of course does not mean that under certain circumstances the lymphocytes could not become modified/

modified and assume the characteristics of monocytes, as is contended by Maximow & Bloom.

RELATION OF THE APPEARANCES IN L. MONOCYTOGENES INFECTION TO THOSE IN NATURALLY OCCURRING DISEASES OF THE RETICULO-ENDOTHELIAL SYSTEM.

The results of artificial stimulation of the reticulo-endothelial system may be compared to the appearances in certain of the diseases already described above. At a comparatively early stage of infection, the production of macrophages in the sinuses suggests the open type of sinus catarrh, later R.14.7 the appearance in the cortical follicles approximated to those of follicular hyperplasia. In the artificial type of hyperplasia the degree of erythrophagocytosis is more intense than that commonly seen in sinus catarrh, and is more reminiscent of that seen in 19/46, and to a less extent in 101/39, i.e. acute reticulosis. The hyperplastic free basophil cells resemble those seen in 264, in which they were not so numerous, but in which their appearance was associated with an increase of monocytes in the circulating blood. The appearances also resemble to some extent those of 16512, though here the peripheral monocytosis was much more intense, and this was reflected in the large number of obvious monocytes throughout the reticulo-endothelial system. Macrophages were not numerous.

It may therefore be stated that the appearances

of/

of the reticulo-endothelial system in L. Monocytogenes infection, in its fully developed state, resembles that of an acute reticulosis with some degree of maturation to monocytes, with the production of numerous erythrophagocytic macrophages and ultimately with a tendency towards fibrosis. Some observers, notably Oberling & Guerin 1934 are of the opinion that at least some types of acute reticulosis are due to infection, and though no casual organism has as yet been isolated, the possibility of a filter passing virus has been considered by these workers.

SUMMARY.

The composition of the reticulo-endothelial system, the derivation of its elements from primitive mesenchyme and the part played by these elements in the storage of vital dyes and in haematopoiesis are briefly reviewed.

The inter-relationship of the elements of the reticulo-endothelial system, their common origin are then considered, in relation to their developmental potentialities and possible lines of differentiation.

Various classifications of the disease processes affecting the reticulo-endothelial system are then discussed and a working classification adopted.

Examples of certain of these disease processes are cited and/

and their inter-relationship is discussed.

The effects of stimulation of the reticulo-endothelial in rabbits, by the Listerella monocytogenes is described and the relationship of the appearances to certain of the diseases naturally affecting the system are considered.

CONCLUSIONS.

Two important elements of the reticulo-endothelial system are:-

(a) The reticulum cell which is found throughout the system, particularly in the stroma of the lymphatic glands, the Malpighian bodies and the pulp of the spleen and, though less prominently, in the bone marrow. This cell is very primitive and possesses the fullest developmental potentialities.

(b) The endothelial cell which is also met with throughout the system, especially in the lymph sinuses of the lymphatic glands, and the blood sinuses of the spleen, the liver (Kupffer cells), and the bone marrow. This cell is closely related to the reticulum cell but is slightly more mature and consequently possesses fewer developmental potentialities tending to differentiate mainly in the direction of phogocytes. There is evidence that both the reticulum cell and the endothelial cell may give rise to monocytes.

Disease processes affecting the reticulo-endothelial system generally/

generally fall into one of four groups viz.

(a) Storage reticuloses. In this group the disease processes do not primarily affect the reticulo-endothelial system, the changes therein being secondary to a metabolic disturbance.

(b) Reactive Reticuloses. Here proliferative changes involve first the endothelial cells and thereafter the reticulum cells, differentiation then occurring, mainly though not invariably in the direction of phagocytes.

(c) Idiopathic Reticuloses. These processes are characterised by proliferation of both reticulum and endothelial cells especially the former. Differentiation may then occur. The greater the proliferation the less the differentiation. In the more chronic forms, differentiation may occur in various directions, towards phagocytes, monocytes, giant cells, fibroblasts, and even cells of the lymphatic and the myeloid series.

(d) Neoplastic Reticuloses. In this group the proliferative process begins locally, very soon spreads widely throughout the reticulo-endothelial system so that it may be difficult to define the primary focus. Distant metastases also occur, Proliferation predominates and differentiation is slight or absent.

Stimulation of the reticulo-endothelial system by means of Listerella monocytogenes produces proliferative changes throughout the system, involving endothelial cells but

more/

more especially reticulum cells. The proliferation is followed by differentiation particularly in the direction of monocytes and phagocytes, the changes resembling those seen in certain of the more acute reticuloses.

Evidence has been adduced that the monocyte may be derived relatively directly from the reticulum cell and that it is rarely and only slightly phagocytic.

The large phagocytes derived from reticulum and/or endothelial cells are quite different in appearance to the monocyte and are actively phagocytic.

Sub-division of the chronic reticuloses into groups depending upon the predominant line of differentiation such as, fibrillary, giant-cell, giant-cell and fibrillary, lymphadenoma etc., while useful for purposes of classification, is not regarded as fundamental, and these conditions are considered to be essentially phases of the same or of closely allied processes.

In the various conditions observed, both naturally occurring diseases and artificial stimulation, the slightness of involvement of the Küpffer cells of the liver has been a noteworthy feature.

Direct production of lymphocytes from reticulum cells has not been observed in the present study.

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# APPENDIX I.

Tables I--XIII.

TABLE I.

| ACUTE RETICULOSES | | | | CLINICAL FEATURES. | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | SEX. | AGE. | DURATION WEEKS. | GLANDS. | SPLEEN. | FEVER. | R.B.C. mil. | W.B.C. | Purpura | Jaundice |
| 101/39. | M. | 39. | 7 | + | -+ | 99-103 | 4.3 | 7000 | -+ | - |
| 19/46. | F. | 57. | 18 | + | --+ | + | 1.61 | 4000 | + | + |
| 264. | F. | 50. | 8 | - | - | + | 1.97 | 7800 | - | -+ |
| 125. | M. | 34. | 9 | -+ | -+ | -+ | 1.79 | 7000 | + | - |
| 16512. | M. | 24. | 9 | + | -+ | 99-102 | 1.85 | 200000 | + | - |

TABLE II.

| ACUTE RETICULOSES. | BLOOD PICTURES. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | R.B.C. | Hb. | W.B.C. | N.P. | S.L. | L.L. | L.M. | Monoblast (S) | Myelocytes. |
| 101/39 | 4.35 | 70 | 7000 | 3990 | 1120 | 840 | 1120 | | |
| 19/46 | 1.61 | 34 | 4000 | 3560 | 320 | | | | |
| 264 | 1.97 | 30 | 7800 | 234 | 741 | 234 | 5460 | 1131 | |
| 125 | 1.79 | 36 | 7000 | | | | | | |
| 16512 | 1.85 | 34 | 200,000 | 24,000 | 16,000 | 2,000 | 134,000 | 20,000 | 4,000 |

TABLE III.

| RABBIT I. | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | R.B.C. | Hb. | W.B.C. | N.P. | S.L. | L.L. | L.M. | B. | E. |
| Before Infection. | 5.33 | 105 | 11,000 | 3960 | 6380 | 297 | 253 | 110 | 0 |
| 4 hrs. after. | | | 9,000 | 3600 | 5220 | 0 | 180 | 0 | 0 |
| 24 hrs. " | | 105 | 6,600 | 3300 | 2706 | 0 | 198 | 198 | 198 |
| 48 hrs. " | | 104 | 7,400 | 1850 | 5104 | 464 | 222 | 0 | 0 |
| 72 hrs. " | | | 12,000 | 3960 | 4920 | 120 | 2280 | 240 | 0 |
| 96 hrs. " | 4.44 | 90 | 16,000 | 2592 | 6480 | 1458 | 5184 | 486 | 0 |
| 120 hrs. " | | 88 | 26,000 | 3640 | 8580 | 4680 | 8060 | 520 | 520 |
| 144 hrs. " | 4.11 | 80 | 23,300 | 3029 | 13,514 | 4194 | 2330 | 233 | 0 |

Polychromatophilic staining of the red corpuscles was noted at 48 hrs. From this time onwards nucleated red cells became steadily more numerous in the blood stream.

TABLE.IV.

| Rabbit 9. | | | | | | |
|---|---|---|---|---|---|---|
| | W.B.C. | N.P. | S.L. | L.L. | L.M. | B. |
| Before infection. | 7600 | 5320 | 1900 | 532 | 304 | 228 |
| 12hrs.after. | 4200 | 3108 | 588 | 462 | 42 | 42 |

TABLE.V.

| Rabbit10. | | | | | | |
|---|---|---|---|---|---|---|
| | W.B.C. | N.P. | S.L. | L.L. | L.M. | B. |
| Before infection. | 6800 | 3400 | 2652 | 476 | 136 | 136 |
| 12hrs.after. | 2000 | 1160 | 620 | 140 | 60 | 20 |
| 24hrs.after. | 2200 | 1144 | 836 | 154 | 44 | 22 |

TABLE.VI.

| Rabbit 11. | | | | | | |
|---|---|---|---|---|---|---|
| | W.B.C. | N.P. | S.L. | L.L. | L.M. | B. |
| Before infection. | 9000 | 3780 | 4410 | 630 | 180 | |
| 12hrs.after. | 4600 | 2898 | 1380 | 138 | 23 | 161 |
| 24hrs.after. | 3000 | 1890 | 870 | 120 | 120 | 60 |
| 36hrs.after. | 7600 | 4180 | 2432 | 304 | 380 | 304 |

TABLE.VII.

| Rabbit 12. | | | | | | |
|---|---|---|---|---|---|---|
| | W.B.C. | N.P. | S.L. | L.L. | L.M. | B. |
| Before infection. | 8800 | 4928 | 2816 | 704 | 264 | 88. |
| 12hrs.after. | 5200 | 3276 | 1508 | 208 | 208 | 0 |
| 24hrs.after | 2600 | 780 | 1612 | 182 | 0 | 26 |
| 36hrs.after. | 6400 | 2240 | 3456 | 448 | 128 | 128 |
| 48hrs.after. | 6000 | 2460 | 2160 | 240 | 960 | 180 |

TABLE.VIII.

| Rabbit.13. | | | | | | |
|---|---|---|---|---|---|---|
| | W.B.C. | N.P. | S.L. | L.L. | L.M. | B. |
| Before infection. | 8200 | 3936 | 3936 | 164 | 164 | 0 |
| 12hrs.after. | 5200 | 3276 | 1664 | 52 | 0 | 52 |
| 24hrs.after. | 4400 | 2420 | 1408 | 52 | 88 | 220 |
| 36hrs.after. | 6600 | 2904 | 2904 | 330 | 396 | 66 |
| 48hrs.after. | 6400 | 2368 | 2944 | 384 | 576 | 128 |
| 60hrs.after. | 10600 | 3816 | 4770 | 212 | 1696 | 106 |

TABLE.IX.

| Rabbit.14. | | | | | | |
|---|---|---|---|---|---|---|
| | W.B.C. | N.P. | S.L. | L.L. | L.M. | B. |
| Before infection. | 12500 | 7500 | 1750 | 2000 | 625 | 625 |
| 12hrs.after. | 5800 | 3712 | 1044 | 232 | 232 | 464 |
| 24hrs.after. | 4400 | 2948 | 792 | 132 | 132 | 352 |
| 36hrs.after. | 6600 | 2772 | 1980 | 264 | 1320 | 198 |
| 48hrs.after. | 9600 | 5376 | 1632 | 480 | 1824 | 288 |
| 60hrs.after. | 11600 | 6496 | 1392 | 116 | 3016 | 580 |
| 72hrs.after. | 12000 | 5640 | 2040 | 240 | 3240 | 840 |

TABLE.X.

| Rabbit.15 | | | | | | |
|---|---|---|---|---|---|---|
| | W.B.C. | N.P. | S.L. | L.L. | L.M. | B. |
| Before infection. | 11000 | 7150 | 2420 | 660 | 550 | 220 |
| 24hrs.after. | 5000 | 2900 | 1450 | 450 | 100 | 100 |
| 48hrs.after. | 9300 | 3720 | 2325 | 186 | 2511 | 558 |
| 72hrs.after. | 9600 | 2592 | 2880 | 480 | 3648 | 0 |
| 96hrs.after. | 9000 | 3420 | 2070 | 720 | 2250 | 540 |
| 120hrs.after. | 11500 | 5060 | 3795 | 575 | 1455 | 460 |

TABLE.XI.

| Rabbit.16. | | | | | | |
|---|---|---|---|---|---|---|
| | W.B.C. | N.P. | S.L. | L.L. | L.M. | B. |
| Before infection. | 11700 | 4212 | 4563 | 1989 | 702 | 234 |
| 24hrs.after. | 6700 | 4824 | 1407 | 335 | 67 | 67 |
| 48hrs.after. | 11000 | 2860 | 4840 | 550 | 2310 | 44 |
| 72hrs.after. | 14200 | 4402 | 5254 | 568 | 3834 | 142 |
| 96hrs.after. | 11100 | 2664 | 4554 | 555 | 2992 | 333 |
| 120hrs.after. | 11000 | 2970 | 3740 | 1760 | 2200 | 330 |
| 144hrs.after. | 11000 | 3520 | 4400 | 2530 | 550 | 110 |

TABLE XII.

| RABBIT 19 | | INNOCULATED L. MONOCYTOGENES. 19.11.38. | | | | | |
|---|---|---|---|---|---|---|---|
| | Innoculated Tryphan Blue 1% 10 c.c. | W.B.C. | N.P. | S.L. | L.L. | L.M. | B. |
| 24.11.38. | + | 17,200 | 11,524 | 2064 | 0 | 3268 | 344 |
| 25.11.38. | + | 16,400 | 11,316 | 1968 | 0 | 3116 | 0 |
| 26.11.38. | + | 22,000 | 16,500 | 1760 | 0 | 3740 | 0 |
| 27.11.38. | + | 15,600 | 13,260 | 624 | 156 | 1248 | 312 |

Animal killed. No large mononuclears in the peripheral blood or in the tissues observed to take up the dye.

TABLE XIII.

| RABBIT 20 | INNOCULATED WITH L. MONOCYTOGENES 19.11.38. | | | | | | |
|---|---|---|---|---|---|---|---|
| | India Ink Higgins 50% 3 c.c. | W.B.C. | N.P. | S.L. | L.L. | L.M. | B. |
| 24.11.38. | | 11,800 | 4602 | 2006 | 826 | 4366 | 0 |
| 25.11.38. | | 17,500 | 6300 | 5425 | 525 | 5075 | 175 |
| 26.11.38. | + | 13,000 | 5200 | 3510 | 520 | 3510 | 260 |
| 27.11.38. | | 12,900 | 4644 | 5289 | 258 | 2709 | 0 |

Animal killed. Six hours after injection of ink a few of the circulating monocytes contained very scanty granules of carbon.

# APPENDIX II.

## Case Histories.

# ACUTE RETICULOSES.

Case. 101/39. T.B. Male Aet. 39 yrs. Steel Worker.

Admitted. 3;3;39.

Died. 20;3;39.

Complaint; Intermittent pain in wrist and ankle joints for four weeks. Swelling of glands of neck for three weeks.

No previous illnesses of note.

This man was seen as an out-patient on 20;2;39 when he presented the features mentioned above. The blood count was:- R.B.C. 5·2 mil. Hb. 80%. W.B.C. 8000/cmm. On admission there was generalised glandular enlargement, the cervical and axillary groups being especially involved. The spleen was just palpable, the liver was not obviously enlarged, He complained of severe joint pains especially in the ankles. There was a brownish rather scaly macular rash on the trunk.

Blood Count. R.B.C. 4·35 mil. Hb. 70%. W.B.C. 7000/cmm. N.P.57% L.L. 12%. S.L. 16%. M. 16%. Paul Bunnel Test Negative. Wassermann Reaction Negative. Biopsy of a cervical gland on 13:3:39, revealed a very cellular process, of apparently malignant nature, and a diagnosis of lymphosarcoma was suggested. The glands rapidly increased in size, he became progressively weaker and died on 20:3:39. During the period in hospital the temperature was irregular varying from 99' to 103'F.

Post Mortem./

Post Mortem. There was generalised glandular enlargement. The glands were discrete, pinkish in colour and soft in consistence; the cut surface was flecked with blood. The spleen was slightly enlarged (260g.) and was soft in consistence and of a dark purplish colour. It gave a strong reaction for iron. The liver (2000g.) was of a uniform rather cafe-au-lait colour and also gave a strong reaction for iron. The kidneys were pale, the capsules stripped easily. There were numerous small pale areas scattered throughout the cortex. The supra-renal glands were slightly larger than normal and appeared to be infiltrated by a neoplastic process. The bone marrow (right femur) was mainly fatty there being no obvious cellular extension.
Histology. Lymphatic gland. The normal structure was completely lost. Only a few lymphocytes were to be seen, scattered here and there. The gland was uniformly cellular, the cells being large with fairly copious neutrophil protoplasm. In general the cell outlines were distinct and there was little or no tendency to syncytial formation. The nucleus was rounded or indented and pale, the chromatin being arranged either in a few strands radiating from the single nucleolus or in a few cases, forming fine scattered granules in the nucleus. There was a clearly outlined nuclear rim. These cells packed the stroma though individual cell outlines were clear, and the great majority were free. Many similar/

similar cells were also free in the lymphatic sinuses. Mitotic figures were fairly numerous. In the lymphatic sinuses there were a number of red corpuscles and also of large macrophages with copious acidophil protoplasm which were actively erythrophagocytic. Reticulin fibrils were fairly copious and separated the type cells into groups of six to twelve but there was no evidence of a close relationship between individual cells and the fibrils which appeared to be rather the remains of the normal reticulin of the gland.

Bone Marrow. In the cellular areas the cells were very uniform the type cell being similar to that met with in the lymphatic glands. The majority of the cells were free though a few appeared to be fixed. In some of the sinuses swollen endothelial cells were to be seen, which closely resembled the type cell in appearance.

Spleen. The Malpighian bodies were small, their central portion was lymphocytic, but towards the periphery were large cells of the same appearance as those in the lymphatic glands, and marrow were to be seen. They appeared to be mainly inside the sinuses at the periphery of the Malpighian bodies, which were opener and more apparent than normal. In the sinuses some of the endothelial cells were swollen and though still fixed, closely resembled the type cell. There

was/

was no noteworthy change in the splenic pulp.

The kidneys showed widespread infiltration with the type cell, mainly around the blood vessels extending into the cortex from beneath the capsule.

The liver showed very little, if any, infiltration.

The suprarenal glands were extensively infiltrated by cells with the characteristics of the type cell.

Case. 19/46. A.B. Female. Aet. 51 yrs.

Admitted: 8: 11: 45.

Died: 20: 1: 45.

For two months prior to admission she had complained of fatigue and had become pale. At the same time she had noticed swelling of the cervical glands.

On admission there were numerous firm discrete glands in the axillary and cervical regions. Blood count showed Hb. 56%. R.B.C. 2·09 mil. W.B.C. 6800/cm. The red cells showed anisocytosis and poikilocytosis. Their fragility was normal. Sternal puncture showed an erythroblastic marrow.

On 8:1:46 Blood count was Hb. 38%. R.B.C. 1 81 mil. and on 15:1:46 Hb. 34% R.B.C.1·61 mil. W.B.C. 4000/cmm. N.P. 89%. L. 8%. Reticulocytes 24%.

Between 22:12:45 and 16:1:46 twelve exposures to X rays were given. On 15:1:46 jaundice appeared and on 18:1:46/

18:1:46 she became unconscious dying on 20:1:46.

Post Mortem. The appearances were those of a profound anaemia of haemolytic type with an erythroblastic bone marrow. The liver weighed 1500g. and was yellowish in colour. The spleen which weighed 3000g. was of firm consistence and was studded with small white dots. There was some enlargement of the lymphatic glands of the neck groins and mediastinum, the largest being 2·5cm. in diameter.

Histology. There was great overgrowth of reticulum cells and in addition there were large numbers of large eosinophilic cells free in the sinuses of the lymph glands, carrying on erythrophagocytosis. These large cells were frequently laden with red corpuscles and sometimes with brown pigment. Erythrophagocytosis was mainly present in the sinuses. Very little was to be seen in the traberculaes. In parts of some of the glands were areas of early febroblast formation.

Case 125/37. J.W. Male Aet. 34 yrs.

Admitted: 9: 3: 37.

Died. 24: 3: 37.

This man first felt unwell in January 1937. His main complaints being increasing weakness and breathlessness.

On admission he was profoundly anaemic. Hb. 36%. R.B.C.1·79 mil. W.B.C. 7000/cmm. There were numerous purpuric/

purpuric spots on the limbs and trunk. There was high irregular pyrexia and his condition rapidly deteriorated.

Post Mortem. There was considerable emaciation. The pericardium presented numerous petechialhaemorrhages and there were also haemorrhages beneath the endocardium. The lymphatic glands in the hila of the lungs were moderately enlarged. Scattered haemorrhages were present on the peritoneum. The mesenteric glands were slightly enlarged and discrete. The liver (1760g) was pale but otherwise appeared to be normal. The spleen (340g.) was firm and purplish in colour. The femoral bone marrow was red throughout the length of the bone, that of the ribs and vertebrae was pale.

Histology. Lymphatic glands. There was no attempt at follicular arrangement, the whole tissue being overrun with small lymphocytes. In the lymph cords there were numerous larger cells with a rather darkly staining nucleus. Typical reticulum cells were not numerous. In the lymphatic sinuses there were a considerable number of large acidophil phagocytic cells.

Spleen. The Malpighian bodies were small and ill-defined and were composed of lyphocytes and of larger cells similar to those seen in the lymphatic glands, At the periphery of the Malpighian bodies, the larger cells were spreading into the splenic pulp which was very cellular with swelling of the/

the sinus endothelium and with many free cells similar to those in the Malpighian bodies. Erythrophagocytosis was prominent in the sinuses and to a less extent at the periphery of the Malpighian bodies.

Bone Marrow. There was great cellularity and among the cells, a proportion resembled the large type seen in the lymphatic glands, the Malpighian bodies and the splenic sinuses.

Liver. There was some periportal infiltration with a tissue composed of lymphocytes, of cells of the large type already noted and of cells which though mononuclear were of almost giant proportions.

Case 264/45. J.T. Female Aet. 50 yrs.

Admitted: 4:10;45.

Died: 21:10:45.

This woman was in good health until August, 1945 when she began to suffer from dyspnoea on exertion. She also developed a dull pain under the left scapula aggravated by deep breathing. Her general condition steadily deteriorated and she became extremely anaemic. A few small glands were paipable in the neck. Seven days before death jaundice appeared. At this time blood count was:- R.B.C. 1·97 mil. Hb. 40%. W.B.C. 7800/cmm. N.P. 3%. S.L. 9·5%. L.L. 3%. Monocytes 70%. Monoblasts 13·5%.

Megaloblasts 1%

Sternal/

Sternal puncture yielded a marrow with large numbers of large mononuclear cells with the features of monocytes.

Post Mortem. An obese female subject. Apart from the findings of a severe anaemia, the following features were noted.

Spleen. (120g.) appeared normal.

Liver. Not enlarged. Showed numerous greyish areas.

Bone Marrow. The medulla of the femur was yellow throughout, that of the sternum was pinkish.

Lymphatic Glands. A number of glands 1-1 5cm. in diameter formed a chain along the posterior border of the sternomastoid muscles. There was no obvious enlargement of the glands of the mediastinum, mesentery or pelvis.

Histology. Lymphatic Gland. The normal structure was obscured. The bulk of the cells were small having the appearance of small lymphocytes. Scattered throughout the gland, in its substance, and also in the sinuses, were fairly numerous larger cells. The cell outline of these large cells was slightly irregular and their protoplasm was moderate in amount and of neutrophil staining reaction. The nucleus, which was relatively large, was generally round but occasionally was indented. The nuclear chromatin was rather fine and a nucleolus was rarely present. A few of these cells

were/

were observed in mitosis. The cells were not observed to be phagocytic. A few similar cells were noted in the blood capillaries of the glands.

Spleen. The Malpighian bodies were small and ill-defined. In the sinuses of the pulp there were numerous instances of erythrophagocytosis and numerous cells laden with brown pigment were present, some free in the sinuses, and some apparently fixed in the walls. The structure of these cells was quite obscured by the pigment. Also in the sinuses, there was a number of large free cells with no pigment and closely resembling those seen in the lymphatic glands.

Liver. No cellular infiltration could be detected. The Kupffer cells were moderately prominent and some contained scanty brownish pigment. None of the Küpffer cells were noted to be free.

Kidneys. No infiltration was detected and the organs were apparently normal.

Case. 16512. J.L. Male Aet. 24 yrs. Student.

Admitted: 30:11:36.

Died: 8:12:36.

Two months before admission he had, what was thought to be influenza, characterised by fever, malaiseand pains in the joints and limbs. At the same time he noticed some swelling of the cervical glands, this was attributed to dental/

dental sepsis and two weeks before admission two teeth were removed. Extraction was followed by copious bleeding.

On admission he was very pale, the cervical glands were much enlarged. The mouth was very foul with ulceration of the gums. The sockets of the recently extracted teeth were very unhealthy and showed no signs of healing. Swabs from the gums yielded a varied flora. The spleen was just palpable. Wassermann reaction was negative. Blood count. R.B.C. 1·85 mil. Hb. 34%. W.B.C. 20,000/cmm.

During the week which he spent in hospital his condition rapidly deteriorated. There was irregular pyrexia up to 104'F. and repeated epistaxes occurred. The white cell count steadily increased viz:-

| | W.B.C. | N.P. | L.L. | S.L. | Myeocytes | Monocytes. Immature | Mature |
|---|---|---|---|---|---|---|---|
| 1:12:36. W.B.C. | 76,000 | 23 | 1 | 11 | 3 | 20 | 42. |
| 2:12:36. | 95,000 | 11 | 0 | 11 | 0. | 20 | 58. |
| 5:12:36. | 193,000 | 15 | 0 | 12 | 3 | 16 | 54. |
| 6:12:36. | 170,000 | - | - | - | - | - | -. |
| 7:12:36. | 200,000 | 12 | 1 | 8 | 2 | 10 | 67. |

The large mononuclear cells were of the usual appearance. Their protoplasm was pale blue with occasional vacuolation. The nucleus was indented and the chromatin was arranged in fine interlacing strands. In a large proportion of the cells, one or more nuclei were present. The cells were oxydase negative. The Paul-Bunnell test was negative.

Post Mortem. The body was that of a well-developed young man. There/

There were numerous small purpuric spots on the trunk. The pericardium showed small petechial haemorrhages. The heart was normal as were the lungs apart from oedema. There was moderate enlargement of the lymphatic glands of the hila of the lungs. The mediastinal glands were also enlarged as were those of the cervical, axillary and mesenteric groups. The enlargement was of only moderate degree, few of the glands being larger than a bean. They were discrete, firm and their cut surfaces were greyish in colour and were often flecked with small red haemorrhages.

Liver. (2200g.) was pale and no infiltration could be made out.

Spleen. (410g.) The consistency was firm and the cut surface was of a uniform dull red colour. The Malpighian bodies could not be identified. The bone marrow of the vertebrae was pale and no areas of infiltration could be detected. In the femur the marrow was pale and gelatinous with a few scattered reddish foci.

The kidneys and the brain appeared normal.

Histology. Lymphatic Glands.qA few lymphocytic foci were still present in the cortical zone. Elsewhere the entire structure of the gland consisted of larger cells generally somewhat oval in shape with their protoplasm frequently drawn out into fine processes which united with the processes of neighbouring cells to form a delicate cellular network.

The/

The cell protoplasm was moderate in amount and faintly basophilic. The nucleus presented a delicate structure. There was a distinct nuclear rim, a nucleolus was generally present from which the chromatin radiated in a series of fine strands. In many instances the nucleus was indented and the chromatin, instead of being arranged in radiating strands, formed a fine interlacing meshwork. In such a nucleus a nucleolus was often present though not invariably. In areas where it was possible to recognise it, the sinus endothelium could also be seen to be swollen. The swollen endothelial cells presented a nucleus of one or other of the types already described. There were also numerous free cells in the lymphatic sinuses, whose appearance strongly suggested that they were monocytes. Numerous typical monocytes were also present in the blood vessels of the substance and of the capsule of the glands.

It was difficult often to identify with certainty the lymphatic sinuses, as the reticular arrangement of the cells throughout the gland formed so many new spaces in which cells might lie free, but in a few areas cells could be seen forming a network in the sinuses.

Reticulin fibrils were scanty throughout the substance of the gland.

Spleen. The Malpighian bodies were indistinct and what remained of them was composed of a few lymphocytes with larger cells/

cells of the types already described in the lymphatic glands, at the periphery. The chief change was in the splenic pulp. The sinuses contained relatively little blood, the endothelial cells were much swollen giving the pulp a solid appearance. The swollen endothelial cells resembled those of the lymph sinuses of the lymphatic glands. Many of the cells were free in the splenic sinuses. The free cells were round with either a round or an indentednucleus. In some the nucleus was of the pale type with a nucleolus and a distinct nuclear rim, in others the nucleus was darker and more uniform though still presenting a nucleus. A proportion of the cells had the typical appearance of the blood monocyte and had no nucleolus.

Bone Marrow. The gelatinous marrow from the femur was highly cellular, the cells conforming to the varieties already described in the spleen and lymphatic glands.

Liver. There was a rather diffuse infiltration along the portal tracts and to a less extent throughout the liver capillaries with cells with the characteristics of monocytes.

# CHRONIC RETICULOSES.

Case. 308/37. H.McM. Male Aet. 45 yrs. Chauffeur.

Admitted: 2:8:37.

Died: 5:8:37.

For six years he had been aware of a soft lump in the right groin and for two years he had suffered from epigastric pain at intervals. On admission he was moderately emaciated and slightly jaundiced and there was a discharging sinus in the right groin below Pouparts ligament. There was irregular pyrexia up to 103'4'F. Blood Count was R.B.C. 4·5 mil. Hb. 70%. N.P. 75%. L.L. 14%. S.L. 8%. L.M. 3%. His condition deteriorated very rapidly and he died on 5:8:37.

Post Mortem. The liver was greatly enlarged weighing 3800g. Scattered through its substance were numerous small red discrete areas.

The spleen (1100g.) was pinkish red in colour and the Malpighian bodies were distinct. The kidneys also were enlarged (Rt. 260g. Lt. 280g.) and throughout the cortices were many small pink areas. The retroperitoneal glands were grossly enlarged and their cut surface was soft, bulging and flecked with blood. The inguinal and axillary glands were also enlarged, the left inguinal glands forming a lobulated mass, those on the right had broken down and there was a discharging sinus.

Histology. Lymphatic Glands. There was great cellularity, the majority of the cells being small lymphocytes. There was a considerable amount of fibrillary eosinophil background.

Reticulum/

Reticulum cells were numerous. Other cells similar in structure to the reticulum cells but much larger were present generally lying in spaces in the tissue. Although in some instances very large these cells had but a single nucleus of pale vesicular type with a single nucleolus. Argyrophil reticulin was copious forming a meshwork throughout the gland recalling the appearance in 'lymphadenoma'.

Liver. There was cellular periportal infiltration. Some of the cells were lymphocytes and some larger resembling in their characteristics reticulum cells. No giant cells were seen. Reticulin fibrils were numerous in the areas of infiltration.

Soleen. The Malpighian bodies were large and composed mainly of lymphocytes among which were fairly numerous reticulum cells. There was much fibrosis of the pulp rendering the sinuses prominent. The sinus endothelial cells were swollen. Argyrophil reticulin was copious throughout the spleen.

The appearances ~~suggested~~ pointed to a hyperplasia of reticulum cells with differentiation to fibrils both argyrophil and collagenous and with a considerable production of uninuclear giant cells.

Case. 103/39. P.P. Male. Aet. 61 yrs.

Admitted: 20:2:39.

Died: 21:3:39.

In/

In January, 1938, an enlarged gland, considered to be tuberculous, was removed from the neck. Thereafter he remained well until January, 1939 when enlargement of the glands in both axillae, neck and groins occurred. On admission there was generalised enlargement of the superficial lymphatic glands which were firm and discrete. The liver was slightly enlarged and there was a tender mass in the epigastrium. The blood showed some anaemia but no other abnormality. A gland was removed and its appearance regarded as typical of lymphadenoma. His condition deteriorated rapidly and he died on 21:3:39.

Post Mortem. The body was emaciated. There was generalised enlargement of the lymph glands. The enlargement was moderate and the glands were in the main discrete. The heart showed brown atrophy. The mediastinal glands were greatly enlarged and on the left side a growth of whitish tissue was connected to the bronchial glands. There was also great enlargement of the para-aortic glands which formed a mass the size of an orange around the coeliac axis and superior mesenteric artery, fromthis mass a tumourlike enlargement of the glands extended downwards on either side along the common iliac arteries where the enlargement gradually diminished.

The liver (1100g) showed some fatty change and scattered throughout it were numerous white areas, some minute, some as large/

large as a pea. One nodule was as large as a marble. The spleen (400g.) was dark red in colour and was studded with white nodules and streaks. In the lumbar vertebrae there were numerous whitish nodules but none could be detected in the demoral marrow.

Histology. Lymphatic Glands. Some areas were cellular, others relatively acellular. There was great overgrowth of the reticulum cells. Giant cells.

Case. 108/39. P.W. Male Aet. 44.

Admitted: 25:1:39.

Died: 23:3:39.

In November he suffered from a 'chill' with pains in the back and down both legs. He began to feel weak and on examination was found to have a low white cell count (2000/cmm.)

On admission the axillary glands were enlarged and the spleen was readily palpable. The white blood count remained low with a slight increase of eosinophils at first. During the period in hospital there was irregular pyrexia and shortly before death jaundice appeared. A gland was removed and the appearances suggested a diagnosis of lymphadenoma.

Post Mortem. The body was well nourished and slightly jaundiced. The axillar glands were enlarged. The mediastinal glands were also moderately enlarged and discrete. The cut surface of the glands was uniformly white.

The/

The liver (2000g.) was pale brownish in colour and throughout its substance there were scattered reddish and also pale areas. The spleen (700g.) was red and rather soft, it presented several infarctions and also diffuse white areas of infiltration. The femoral bone marrow was red throughout the length of the bone.

Histology. Lymphatic Glands. The normal structure was entirely lost. It was replaced by a fine pinkish reticulum which was fairly cellular. Most of the cells had the appearance of reticulum cells but there were a few giant cells, some uninuclear and some multinuclear. Argyrophil reticulin was copious and coarse.

Similar reticulated tissue with scanty giant cells was diffusely scattered throughout the liver and also composed the white areas in the spleen.

The upper two thirds of the femoral marrow was red with greenish white gelatinous areas.

The central nervous system was normal.

Histology. Lymphatic Glands. In places the same gland showed areas almost completely converted to cellular fibrous tissue whereas other areas were very cellular. In the cellular areas the reticulum cells were increased in number and prominence. There were many giant cells, usually profecting into small spaces but apparently fixed. Some such cells were of very great size. The nucleus of the giant cells was usually single but often greatly convoluted. It was darker than the nucleus of the ordinary reticulum cell but cells with nuclei intermediate in their/

their characteristics between the reticulum cell and the giant cell were also to be seen. Although there was a considerable amount of argyrophil reticulin it was mainly confined to the capsule of the gland and was almost completely absent in the cellular areas even in the fibrous portions it was scanty. Bone marrow. In places there was a cellular fibrous tissue similar to that in the glands though there were also cellular areas. Giant cells mainly uninuclear were fairly numerous. Argyrophil reticulum was very scanty. Spleen. The central parts of the Malpighian bodies were clearly demarcated from the pulp. The lymphocytes of the Malpighian bodies were largely replaced by larger cells of the reticulum type with some giant cells. At the periphery the tissue had become of a cellular fibrous type and passed gradually into the pulp. A few giant cells were present at the edges of the Malpighian bodies. Argyrophil reticulin fibres were not prominent though protoplasmic fibres were very numerous.

The whitish nodules in the liver were periportal in situation and were composed of the same two types of tissue as the lymphatic glands viz. cellular and fibrous.

Case 446/37 - J.C. Male. Aet. 46 yrs. Hammerman.

Admitted: 7.10.37.

Died: 28:11:37.

In April, 1937, he began to suffer from nausea and vomiting. By/

By June, 1937, he was conscious of failing appetite and had suffered a considerable loss of weight.

On admission he was extremely ill with enlargement of the lymphatic glands of axillae neck and groins and a mass could also be felt in the left iliac region. The liver and spleen were enlarged.

He also suffered from silicosis.

On 16th October, 1937, a gland was removed from the groin and the condition was diagnosed as lymphadenoma. He then received six exposures to deep X rays. His condition deteriorated and shortly before death he became jaundiced.

Post Mortem. The body was emaciated and jaundiced. The heart showed brown atrophy and the lungs were affected by silicosis but there was no evidence of tuberculosis.

The cervical, axillary and mesenteric glands were enlarged and discrete. The liver (2500g.) was enlarged, dark red in colour and presented areas of infiltration with whitish tissue. The glands in the porta hepatis were much enlarged.

The spleen (700g.) was firm with numerous small scattered white nodules. The lymphatic glands around the head of the pancreas were much enlarged and formed a matted mass.

The kidneys appeared normal.

The vertebral bone marrow showed numerous areas of whitish infiltration, the upper two-thirds of the femoral marrow was red with greenish white gelatinous areas.

The/

The central nervous system was normal.

Histology. Lymphatic glands. In places the same gland showed areas almost completely converted to cellular fibrous tissue, whereas other areas were cellular. In the cellular areas the basic reticulum cells were increased in number and prominence. There were numerous giant cells usually fixed but projecting into spaces. Some such cells were of great size. The nucleus of the giant cell was usually single but often greatly convoluted. It was darker than the nucleus of the ordinary reticulum cell, but cells with nuclei intermediate in their characteristics between the reticulum cell and the giant cell were also to be seen. Argyrophil reticulin was fairly copious in the cellular part of the gland where it formed a honeycomb. In the fibrous portions it was in very small amount.

Bone marrow. In places there was cellular fibrous tissue similar to that in the lymphatic glands, there were also fairly numerous giant cells mainly with a single nucleus. Argyrophil fibrils were scanty.

Spleen. The central parts of the Malpighian bodies were clearly demarcated from the pulp. The lymphocytes of the Malpighian bodies were largely replaced by larger cells of reticulum type with some giant cells. At the periphery the tissue had become of cellular fibrous type and merged gradually with the pulp.

The liver contained numerous nodules, periportal in situation, partly cellular and partly fibrous.

Case 169. Male. Aet. 27 yrs. Glasscutter.

Admitted: 11: 3:38.

Died: 11: 5:38.

For a year prior to admission he complained of indigestion with pain occurring almost at once after food. His general condition gradually deteriorated and shortly before admission the glands of the neck commenced to swell.

On admission he was pale weak and emaciated and the glands of the neck were generally enlarged. The liver and spleen were also enlarged. During the next two months his condition rapidly deteriorated and he ran an irregular fever up to 102°F. There was a professive anaemia.

Blood. 11:3:38. R.B.C. 4.96 mil. Hb. 70.

10:5:38. R.B.C. 2.07 mil. Hb. 30.

Post Mortem.

The body was greatly emaciated and there were a few petechial spots on the trunk. There was general enlargement of/

of the lymphatic glands both superficial and deep, those of the mediastinum being especially large. Liver. 1950g. was congested but presented no othe obvious abnormality. The spleen, 900g. was grossly enlarged and presented several areas of whitish tissue. The left kidney also showed a nodule of white tissue at its lower pole. The bone marrow of the vertebrae was infiltrated by a whitish tissue, that of the femur was yellow and gelatinous with a few areas of white tissue.

Case 15950 - J.C. Male. Aet. 37 yrs.

Admitted: 13: 8:35.

Died: 25: 9:35.

This patient was in good health until July, 1932, when he noted swelling of the cervical glands. One gland was removed and examined but the result is unknown. Following this biopsy all the cervical glands were removed as far as possible. Thereafter he remained at work till March, 1935, when he became debilitated and enlargement of the glands of the left side of the neck was noticed. Following biopsy a diagnosis of lymphadenoma was made. He developed a cough with slight haemoptysis.

On admission to hospital, he was pale and thin, there was slight icterus and the cervical, axillary and mediastinal glands were enlarged. The liver and spleen were also enlarged. While in hospital there was pyrexia up to 102°F. and his condition rapidly deteriorated.

Blood/

Blood Count. 13:8:35. R.B.C. 4 mil. Hb. 60% W.B.C. 20,000/cmm.
with polymorphon clears predominating.
28:8:35. R.B.C. 2·75 mil. Hb.

Post Mortem. The body was moderately nourished and there was slight oedema of arms and legs. Generalised glandular enlargement was present. The mediastinal glands were particularly involved on the right side, whence white tumour-like tissue extended into the hilum of the lung. The abdominal glands were much enlarged especially the para-aortic group. On section the glands were white and firm.

The liver (2100g.) showed diffuse infiltration with small white nodules.

The spleen (200g.) was firm and presented numerous white areas.

The kidneys which were of normal size showed a few areas of white infiltration in their cortices.

Histology. Lymphatic Glands. The normal architecture was completely destroyed and except for a narrow rim of lymphocytes at some portions of the periphery, these cells were scanty. There was an underlying network of pinkish fibres extending from the cell bodies. The cells were of the reticulum type with large pale nucleus in which there was a single nucleolus with scanty chromatin arranged in a few radial strands. There was a definite nuclear rim. The branching processes of these cells gave the tissue a honeycomb appearance. Here and there

were/

were larger cells which generally bulged out into a small space; the nucleus of these larger cells was frequently lobulated but retained the same chromatin pattern as the smaller more numerous cells. Rarely there were two nuclei. In the deeper parts of the glands the tissue was less cellular and many of the cells tended to be of the fibroblastic type. Finally in some areas it consisted of a fibrillated eosinophil matrix with scattered elongated nuclei. In the cellular areas there was a large amount of argyrophil reticulin arranged in a honeycomb fashion and in close relationship to the cells. In the more fibrous areas reticulin was scanty.

Similar cellular tissue was present around the portal tracts of the liver and also in the Malpighian bodies of the spleen but in these situations fewer giant cells were to be seen. Many of the Malpighian bodies were completely fibrosed. The pulp was very cellular, the sinus endothelial cells being much swollen but few being free in the sinuses. There was considerable evidence of erythrophagocytosis particularly around the fibrosed Malpighian bodies where there were some large cells stuffed with brown pigment.

Case 944/38 - Mrs. G. Gland removed at biopsy. Histology. The follicular arrangement was completely lost. The tissue was composed largely of enlarged reticulum cells.

The/

The cells were mainly of moderate size and had a single nucleus but there was a considerable number of giant cells also usually uninuclear, some lying free in spaces in the tissue and some apparently fixed. Their nucleoli had usually a single prominent nucleolus. The smaller cells had relatively copious protoplasm which was drawn out into rather coarse processes which united with those of neighbouring cells to forman eosinophilic groundwork. Argyrophil reticulum was copious and was arranged in a honeycomb fashion. The large cells appearing to be perched on the fibrils.

Case 1242/39 - M.McK. Male. Aet. 26 yrs. Gland removed at biopsy.

The gland showed a great overgrowth of reticulum cells throughout its substance. In the sinuses there were also numerous branching cells of reticulum type and the sinus endothelial cells were also swollen. Giant cells were fairly numerous and were mainly uninuclear. Their nucleus was round or indented and had a distant dark rim. In the swollen endothelial cells the nuclei appeared to become darker as the cells enlarged and the nuclear chromatin became coarser. Some of the reticulum cells in the sinuses were free. The general picture resembled to some extent that seen in case 16512, monocytic leukaemia but argyrophil reticulin fibrils were numerous thoughless so than is usual in typical lymphadenoma.

Case/

Case 34/37 - C.G. Lymphatic gland removed at biopsy.

There was great overgrowth of reticulum cells with typical pale nuclei. Some of these cells were of great size although possessing only a single nucleus. In a few instances these large cells were undergoing mitotic division. In the sinuses the endothelial cells were swollen and branching cells of reticulum type were also present traversing the sinuses. A number of the cells were free in the sinuses. Argyrophil reticulin fibrils were numerous forming a honeycomb.

Case 477/37 - A.A. Male. Aet. 32 yrs. Coal carter.

Admitted: 27:10:37.

Died: 18:12:37.

In August, 1937, he began to complain of tightness in the chest and general weakness.

On admission he was anaemic and the spleen was slightly enlarged.

Blood count showed:- R.B.C. 3·02 mil. Hb. 64%. W.B.C. 8600/cmm. with lymphocytes 42 5%. His condition rapidly deteriorated and on 17:12:37 the blood count was R.B.C. 1·1 mil. Hb. 25%. W.B.C. 10,200/cmm.

Post Mortem. The liver (2250g.) was pale and showed a fine diffuse infiltration with whitish tissue.

The spleen (1500g.) was grossly enlarged, pinkish in colour and numerous small white areas were scattered through its substance.

The/

The kidneys were pale and there were scattered areas of white infiltration in the cortico-medullary zone.

The femoral bone marrow was of a pinkish colour throughout the length of the bone.

Histology. Lymphatic Glands. The cortical lymphocytes were still arranged to some extent in follicles. Among them were larger cells with pale nuclei sometimes with anucleolus. These cells were free, rounded and their nucleus was large in proportion to their total size. The endothelial cells of the lymphatic sinuses were swollen and a few actively phagocytic large cells were free in the sinuses.

Spleen. The Malpighian bodies were indistinct and presented a fine eosinophilic fibrillary network in which were enmeshed lymphocytes and larger reticulum cells. The pulp sinuses were outlined by similar fine, fibrillary intersinusoidal tissue, were increased in number and were prominent. The sinus endothelial cells were also swollen. There was very little evidence of erythrophagocytosis. In places areas of the pulp were fibrosed.

Liver. There was considerable infiltration with a cellular tissue composed of lymphocytes and reticulum cells.

The kidneys were grossly infiltrated by a similar tissue.

Case 16002 - J.M. Male. Aet. 44 yrs. Clerk.

Admitted: 13: 6:35.

Died: 6:11:35.

For six months prior to admission there had been enlargement/

enlargement of the lymphatic glands of the neck and groin. The enlargement was painless and slowly progressive. During his stay in hospital enlargement of the liver and spleen was noted. Biopsy of a cervical gland revealed a diffuse hyperplasia of the lymphoid tissue. The hyperplastic cells were invading the capsule and the appearances were regarded as suggestive of leukaemia. His condition gradually deteriorated with occasional periods of apparent improvement and death occurred on 6:11:35. The blood showed unusual changes viz:-

| | R.B.C. | Hb. | W.B.C. | N.P. | E. | B. | L.L. | S.L. | L.M. |
|---|---|---|---|---|---|---|---|---|---|
| 10:6:35. | 4 5 | 83% | 7000 | 45% | 25% | 1 3% | 11 6% | 17% | 0 |
| 17:6:35. | | | | 48 | 28 | 1 | 16 | 2 | 6 |
| 1:7:35. | | | | 49 5 | 23 | 5 | 12 | 0 | 15 |
| 12:7:35. | | | | 48 | 20 | 1 | 16 | 2 5 | 12 5 |
| 2:8:35. | | | | 60 | 13 | 2 | 17 | 1 | 7 |
| 8:8:35. | | | | 50 | 28 | 5 | 8 | 3 5 | 10 |
| 15:8:35. | 4 02 | 72 | 6800 | 43 | 36 | 5 | 15 5 | 2 | 3 |
| 22:8:35. | 4 06 | 66 | 6600 | 45 | 10 | 5 | 29 | 5 5 | 10 |
| 3:9:35. | | | | 45 | 4 | 1 | 35 | 0 | 15 |
| 3:10:35. | 2 97 | 56 | 2400 | 33 | 6 5 | 0 | 17 | 16 | 27 5. |

Post Mortem. The body was considerably emaciated. The liver was enlarged weighing 2500g. and was pale with small whitish nodules scattered throughout its substance. The spleen (520g.) was dark with very numerous fine scattered white areas. There was generalised enlargement of the lymphatic glands especially the mediastinal, bronchial and retro-peritoneal groups. The

bone/

bone marrow of the vertebrae and ribs showed numerous whitish patches of infiltration.

Histology. Lymphatic Glands. The normal structure was obscured. There was a coa rse eosinophil groundwork arranged in a series of interlacing fibres. Reticulum cells were numerous and lymphocytes were also present in considerable numbers. The reticulum cells were present in the substance of the gland and many similar cells were free in the sinuses. In the sinuse the cells were round or oval with a round relatively large nucleus usually possessing a single nucleolus. The chromatin was fairly fine. Another type of large cell namely large phagocytes with eosinophilic protoplasm were also present free in the sinuses. Argyrophil reticulin varied from place to place in some areas being fine and scanty and in others relatively copious. Its arrangement however was not characteristic.

Liver. A typical white nodule was found to be sharply demarcated from the liver cells. It was composed of rather scanty reticulum cells with typical vesicular nucleus similar to those seen in the trabeculae of the lymph glands and more numerous rounded cells of the type met with free in the sinuses of the thelymph glands. There was also a groundwork of palish pink fibres. In the nodule the liver cells had disappeared but the bile ducts persisted.

Spleen. The Malpighian bodies were not clearly defined and were comparatively acellular. The cells were lymphocytes and reticulum cells. In/

In the pulp the sinus endothelial cells were swollen.

The haematological findings in this case suggested that large monocytes were being produced in considerable numbers though not so freely as in typical monocytic leukaemia. The histological picture also pointed to the production of cells closely resembling monocytes particularly in the lymphatic glands though to some extent also in the spleen. At the same time there was a good deal of fibre production. Another curious feature was the eosinophilia met with in the earlier stages of the case. The whole picture indeed bears some resemblance to monocytic leukaemia and some to 'lymphadenoma' and the general conclusion is that the fundamental process was a reticulum cell hyperplasia with differentiation in two if not three directions namely to monocytes, to fibres and to large phagocytes.

Case 308/34 - McL. Male. Aet. 18 yrs. Lymphatic gland removed at biopsy.

The gland which was from the groin had been enlarging painlessly for two years.

The gland was cellular the normal structure being completely obscured. A few foci of lymphocytes persisted surrounded by proliferating reticulum cells. Even in the lymphocytic foci there were some large cells with nuclei of reticulum type and with fairly copious protoplasm which was drawn out into processes giving the cells a stellate appearance. The sinus endothelial cells were swollen and many cells of this type/

type were free in the sinuses. Reticulin fibrils were not numerous.

Comment. This gland resembles in some respects nos. C.G. and M.McK. in that there was considerable hyperplasia of the sinus endothelial cells. The whole process however represents a hyperplasia of reticulum cells. Giant cells were absent and little or no differentiation had as yet occurred. The exact nature of the process is not clear. It strongly suggests however the early stages of a reticulosis of the lymphadenoma type.

Case 1319/138 - W.G. Male. Aet. 18 yrs. Lymphatic Gland removed at biopsy.

The normal structure of the gland was largely destroyed but a few cortical follicles persisted. The gland was very cellular, the predominant cell being of the reticulum type with typical pale nucleus and single nucleolus. In some areas there were very large cells with a single nucleus also of reticulum type. Argyrophil fibrils were present but were not so prominent as is usual in lymphadenoma.

Case 2005/38 - Wm. M. Lymphatic gland removed at autopsy. The normal structure persisted to some extent. There was however great overgrowth of reticulum cells, which were invading the lymphoid follicles and replacing the lymphocytes. A few giant cells were to be seen. Argyrophil reticulin fibrils were increased among the reticulum cells but were absent among the lymphocytes.

Case 6/10. Lymphatic Gland removed at biopsy.

The gland was cellular and the proliferative process was at a relatively early stage. The basic tissue consisted of reticulum cells. Giant cells both uninuclear and multinuclear were however numerous. Lymphocytes persisted in scattered foci and eosinophil leucocytes were also prominent. Argyrophil reticulin was fairly copious among the reticulum cells but as usual was absent among the lymphocytes. In places hyperplastic reticulum cells could be seen invading lymphocytic areas.

Case 196/38. Lymphatic Gland removed at biopsy.

There was great increase of the basic reticulum cells with some giant cell formation, the giant cells being generally uninuclear. Lymphocytes were numerous. Considerable numbers of eosinophil cells were scattered throughout the tissue but were not to be seen inside the blood vessels. Agyrophil reticulin was copious in amount. Some of the giant cells were extremely large and resembled megakaryocytes.

Case 1713. Lymphatic Gland removed at biopsy.

The normal structure of the gland was destroyed. There was abasis of reticulum cells and giant cells were numerous. Some had only one nucleus some two or even three. The nucleus was of the pale type with rather scanty chromatin and with a nucleolus. These giant cells appeared to be derived from the swollen endothelial cells of the lymphatic sinuses. They were usually fixed to the wall/

wall of the space in which they were lying but sometime they appeared to be free. Eosinophil polymorphonuclear leucocytes were fairly numerous. Lymphocytes were also fairly numerous in the remnants of the lymphoid trabeculae and also free in the lymphatic sinuses. Argyrophil reticulin was moderate in amount and formed a very fine network which enclosed groups of cells.

Case 176/37 - V.Mc. Female. Aet. 39 years. Icer.

Admitted: 4: 3:47.

Died: 6: 5:37.

In January, 1937, she suffered from influenza and was off work for two weeks, she returned to duty but felt weak and a week later went to bed. During February, 1937, she had three severe epistaxes and was admitted to hospital during a fourth attack.

On admission she was extremely anaemic and the liver and spleen were slightly enlarged. The superficial lymphatic glands were not obviously enlarged.

Blood count:- R.B.C. 770,000/cmm. Hb. 15%. W.B.C. 68,000/cmm. Almost all the white corpuscles were lymphocytes.

On 5th March, 1937, she received a transfusion of 500cc. of blood.

6:3:37 W.B.C. 32,400/cmm.

10:3:37. W.B.C. 7,600''

17:3:37. Transfusion 500cc.

27:3:37. Transfusion 500cc.

3:5:37. W.B.C. 148,000/cmm. Almost all small lymphocytes.

Apart/

Apart from the great increase in small lymphocytes, the blood picture was that of aplastic anaemia. On 6:5:37 she vomited, developed severe epistaxis and died rather suddenly. The axillary and inguinal glands had gradially increased in size during the period in hospital.

Post Mortem. Nutrition was poor. The pericardium showed numerous petechial haemorrhages and the heart was the seat of fatty degeneration. In the stomach there were scattered haemorrhagic erosions.

The liver (1800g.) showed numerous small white areas of infiltration.

The spleen (700g.) was dull red in colour and scattered throughout its substance were numerous white nodules.

The kidneys showed multiple areas of infiltration in their cortices.

The lymphatic glands of the axillae, mediastinum, mesentery and groins were enlarged and discrete and consisted of pinkish soft tissue.

The femoral bone marrow was pale throughout.

Histology. Lymphatic Glands. The normal structure was entirely lost, the glands being overrun with small lymphocytes.

The liver was grossly infiltrated with small lymphocytes especially in the peroportal areas but they were also spreading between the liver cells along the capillaries. The kidneys, particularly/

particularly the renal cortices were also extensively infiltrated with small lymphocytes. In the spleen the Malpighian bodies were greatly enlarged and were composed almost entirely of small lymphocytes. The femoral bone marrow was also composed almost entirely of similar cells.

The appearances in this case are regarded as typical of lymphatic leukaemia. The progress of the case was relatively acute and a noteworthy feature was the early development of severe anaemia of aplastic type in the absence of any therapeutic measures such as X ray therapy. Histologically there was a striking absence of hyperplasia on the part of reticulum cells throughout the reticulo-endothelial system.

Case 55/37 - N.R. Male. Aet. 58 yrs. Steelworker.

Admitted: 28: 1:37.

Died: 12: 2:37.

This patient was admitted with a typical history of angina pectoris. He was anaemic and the spleen was considerably enlarged, the cervical glands moderately so. He died suddenly from coronary thrombosis. The blood count was:- R.B.C. 2 7 mil. Hb. 37%. W.B.C. 90,000/cmm. Almost all the white cells were small lymphocytes.

Post Mortem. A tall well-built man of fair nutrition. The heart showed occlusion of the anterior descending branch of the left coronary artery. The thoracic glands were moderately enlarged,/

enlarged, the abdominal lymphatic glands also showed a moderate general enlargement.

In the stomach there were numerous small haemorrhagic erosions.

The liver (1900g.) presented throughout its substance numerous greyish nodules and streaks.

The spleen (1000g.) was brick red in colour and contained many small greyish nodules.

The bone marrow of the upper third of the femur was greyish pink as was that of the ribs.

Histology. Lymphatic Glands. The follicular structure was entirely lost. The glands were very cellular, the cells being uniform in type and consisting of small lymphocytes. Reticulum cells were not at all prominent nor were immature cells of the lymphoid series to be detected. Considerable numbers of macrophages were present in the sinuses which also contained many red corpuscles. The sinus endothelial cells were swollen. Argyrophil reticulin was inconspicuous.

Spleen. The Malpighian bodies were large and consisted almost entirely of small lymphocytes.

Liver. Infiltration with small lymphocytes was present around the portal tracts whence it spread among the liver cells.

Kidneys. There were numerous areas of lymphocytic infiltration especially under the capsule and around the blood vessels of the cortex.

The pinkish bone marrow of the upper third of the femur consisted almost/

almost entirely of small lymphocytes.

In this case also there was very little reticulum cell hyperplasia immature cells and the lymphoid series could not be distinguished.

# NEOPLASTIC RETICULOSES.

Case 16184 - T.R. Male. Aet. 33 yrs. Miner.

Admitted: 14: 1:36.

Died: 17: 3:37.

For three months prior to admission he had noticed swelling of the cervical glands and for a few days he had experienced spasmodic dyspnoea.

On admission there was some cyanosis of the head and neck and the cervical glands were grossly enlarged. The glands were smooth, hard, discrete and fixed to the deep tissues. No other glandular enlargement was noted nor was the spleen palpable. There were signs of a generalised bronchitis and X ray examination revealed a large mass in the mediastinum.

Blood count was:- R.B.C. 6 mil. Hb. 110%. W.B.C. 15,000/cmm. The white corpuscles were stated to be predominantly small lymphocytes.

After receiving five exposures to deep X rays, the cervical glands almost disappeared and the mediastinal mass was greatly reduced in size. He was discharged on 15:2:36. He was re-admitted on 22:2:36 complaining of abdomina pain. After one exposure to deep X rays the pain disappeared and he was allowed home. He was readmitted on 14:3:36. On this occasion he was extremely ill with generalised enlargement of the lymphatic glands of the axillae, neck and groins. The spleen was much enlarged and fluid was present in the left pleural cavity. X ray examination/

examination showed that the mediastinal mass was still small. Blood count was:- R.B.C. 3 46 mil. Hb. 70%. W.B.C. 15,000/cmm. with small lymphocytes predominating. His condition rapidly deteriorated and death occurred on 17:3:36.

Post Mortem. The lungs were oedematous and in the right lower lobe there was a small fleshy tumour 5 cm. in diameter. The mediastinal glands were considerably enlarged, some being whit on section others haemorrhagic. Scattered over the peritoneum were several small cherry-like nodules which were situated on the peritoneal surface of the intestine. These tumours were firm in consistency and dark red in colour. Arising from the lining of the small intestine were hundreds of dark red tumours, some very small others up to 2 cm. in diameter. They were most numerous in the jejunum, on passing downwards they became less numerous and also smaller. In some places the tumours had sloughed off leaving ulcerated areas. No tumours were present in the colon.

The liver (3950g.) was greatly enlarged and was the seat of chronic venous congestion. In the right lobe there were numerous small red areas usually circular and discrete but occasionally two appeared to have fused. There were fleshy masses of the same red colour in the porta hepatis.

The spleen (2000g.) was bright red in colour and presented several old infarctions, the Malpighian bodies were indistinct.

The/

The right suprarenal gland was almost destroyed by a mass of haemorrhagic and necrotic tissue. On the left the central portion of the suprarenal was occupied by a necrotic mass but apparently normal suprarenal tissue persisted at each pole. The paraaortoic lymphatic glands and those about the head of the pancreas were greatly enlarged forming tumour-like masses. On section they were pale red in colour and soft in consistence.

Histology. Lymphatic Glands. The normal architecture was entirely destroyed. The gland which was very cellular consisted of cells, larger than small lymphocytes, tightly packed together. The individual cell outlines were frequently indistinct. The nucleus had a definite rim and the chromatin was arranged in a more delicate pattern than that commonly seen in cells of the lymphatic series. The cells were divided into compartments by bands of coarse fibrous tissue.

Tumour mass from the duodenum. The structure resembled that seen in the lymphatic glands, but the tissue was not traversed by fibrous tissue.

Liver. The liver tissue was riddled with the type cell. It occurred in foci around the portal tracts but also had spread widely through the capillaries. Where the cells were packed together in foci they tended to become elongated and the nucleo appeared darker, the appearances being that of a very cellular tumour. The tumour masses from the porta hepatis were of similar structure. The small tumour from the lower lobe of the right/

right lung had a similar structure.

The kidneys showed extensive subcapsular infiltration which spread into and broke up the kidney substance extending in a series of prolongations as far as the medulla.

The spleen contained great numbers of the type cell but they were more loosely packed than in the glands.

In the pericardium, chiefly around blood vessels, there were areas of infiltration by the type cell.

Case 15923 - Mrs. B. Aet. 62 yrs.

Admitted: 22:8:35.

Died: 29:8:35.

The chief clinical features in this case were splenomegaly of six months duration, cervical adenitis of three weeks duration and progressive asthenia. The patient was a known diabetic.

On admission X ray examination revealed increase of the mediastinal shadow. Blood count was:- R.B.C. 3 56 mil. Hb. 55%. W.B.C.1800/cmm. The general condition deteriorated rapidly and death occurred seven days after admission.

Post Mortem. A rather obese female subject. There were enlarged glands in the neck and especially in the left supraclavicular region. The mediastinal glands were also enlarged.

The liver (2400g.) was light brown in colour and gave a weak reaction for iron.

The/

The spleen (2300g.) was dull red in colour and soft in consistence. One large infarcation was present.
The kidneys (RT. 260g. Lt. 190g.) presented no special abnormality.
The mesenteric, and more especially, the retroperitoneal glands were greatly enlarged forming a matted mass from which projected a tumour mass embracing the lower pole of the right kidney. A tumour mass was also present in the pouch of Douglas.
The bone marrow of the right femur was pinkish and was mottled with white foci.
Histology. The enlarged glands and the tumour-like masses presented a similar histological picture. The tissue was extremely cellular the cells being of uniform type and relatively large. The nucleus was large in proportion to the size of the cell and its texture was fairly light. The cell outlines were in general distinct, but in places there was a tendency to syncytial formation. Mitotic figures were frequent. A few normal looking basic reticulum cells were to be seen. Thin walled blood vessels were very numerous. Argyrophil reticulin was scanty.
Bone marrow was completely occupied by cells of the type described which showed a tendency to orientate themselves around the fat spaces.
Liver. There were fairly numerous foci of infiltration with the type cell and in addition these cells were diffusely scattered in small numbers throughout the liver capillaries. The Kupffer cells/

cells were unaffected.

Spleen. The Malpighian bodies were indistinct and the pulp was extremely cellular, the cells being of the type met with in the glands, indeed the whole structure of the spleen was completely obscured by those cells. In areas the retroperitoneal tumours and in the lymphatic glands, the cells showed a tendency to orientate themselves around spaces assuming an almost endotheliomatous appearance.

The kidneys showed no infiltration.

Case 800. Male Aet. 48 yrs.

Admitted: 9: 9:38.

Dismissed: 24: 9:38.

Three years before admission a small painless swelling appeared in the groin. It had varied in size since then but never disappeared. A year before admission similar swellings were noticed in the armpits and the neck. Just before admission these swellings began to increase in size rapidly. The glands varied in size from a pea to a pigeon's egg and were discrete, painless rubbery and not hard. The spleen was enlarged two inches below the costal margin. X ray did not reveal any enlargement of the mediastinal glands. The white blood count was 6000/cmm. with 50 per cent lymphocytes.

Whenere 700
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778

# OBSERVATIONS ON CERTAIN DISEASES OF THE RETICULO-ENDOTHELIAL SYSTEM.

BY

ALEX.H.IMRIE.

APPENDIX.III. ILLUSTRATIONS.

Fig.1. 209/35.Sinus Catarrh.
Lymphatic Gland showing sinus catarrh.
H.& E.X 100.

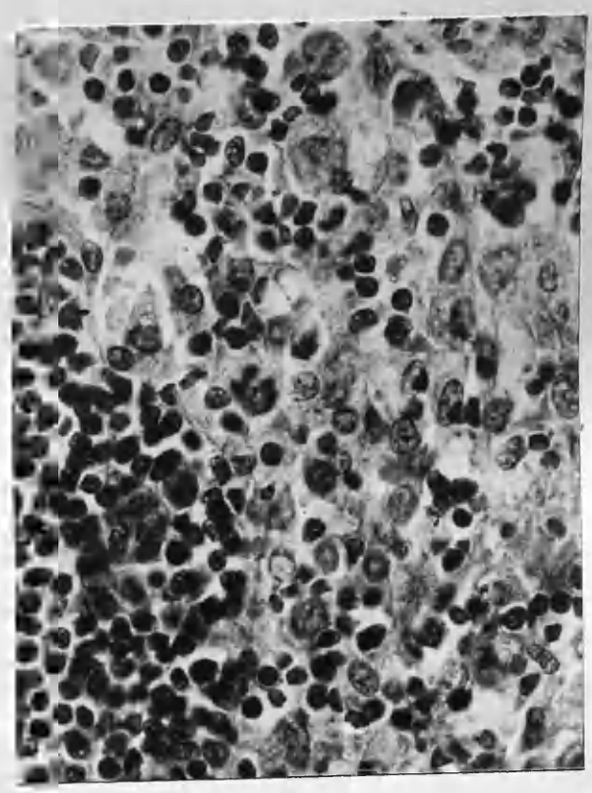


Fig.2. 209/35. Sinus Catarrh.
Showing almost solid arrangement of of ce ls with swelling of endothelium. H.& E.X 500.

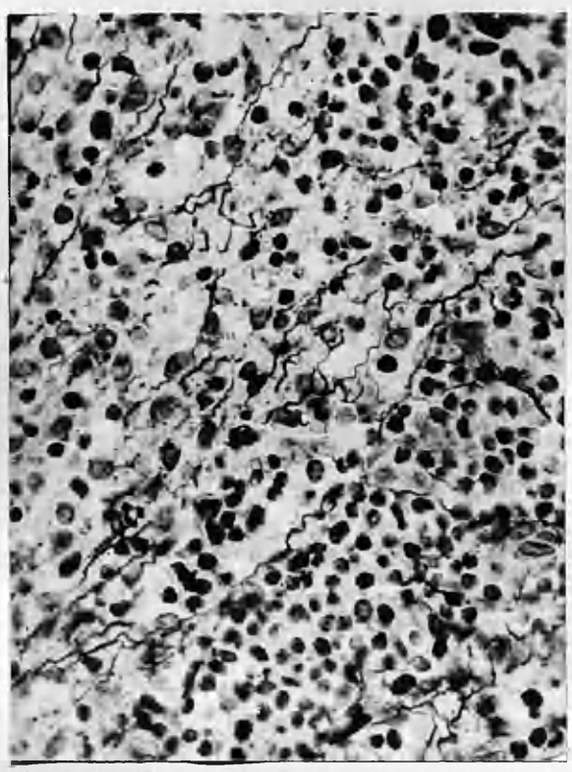


Fig.3.209/35. Sinus Catarrh.
Sinus to show reticulin fibrils.
Silver impregnation.X 400.

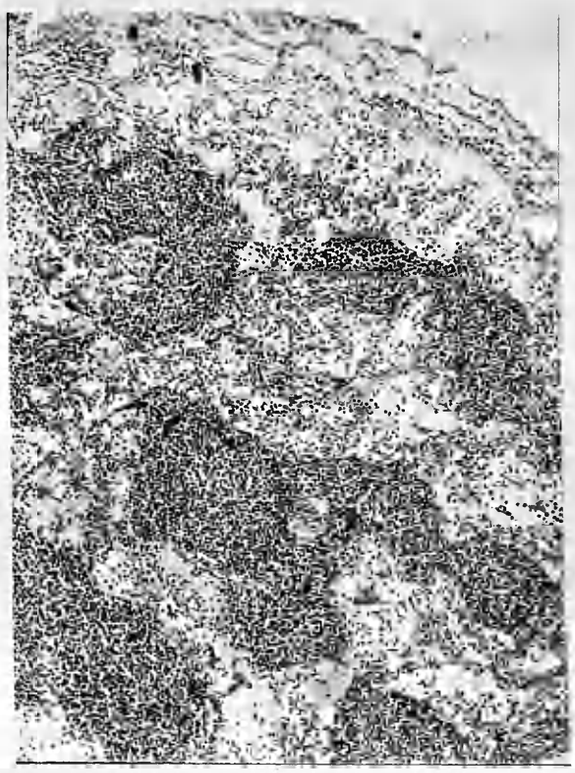


Fig.4. 1267/38. Sinus Catarrh.
Gland showing sinus catarrh of open type.
H.& E.X 100.

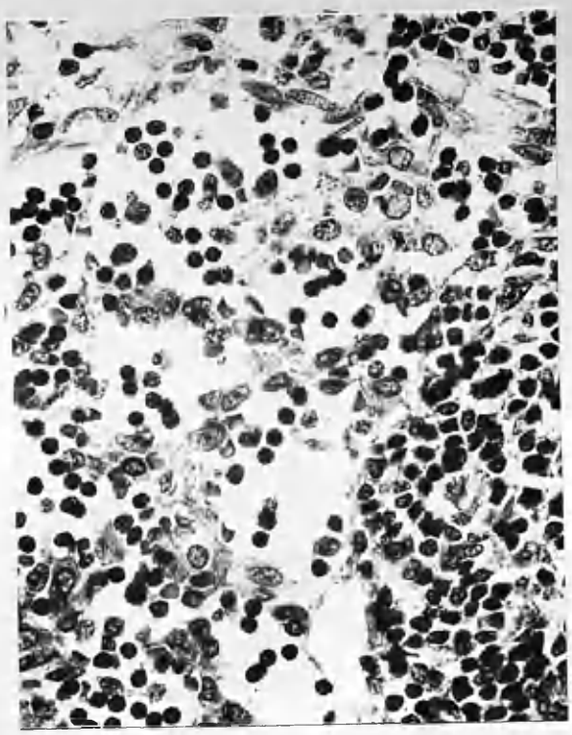


Fig.5. 1267/38. Sinus Catarrh.
Same gland as in Fig.4.
H.& E. × 400.

Fig.6. 461/38. Sinus Catarrh.
Gland showing sinus catarrh of open type with a good deal of blood in the sinuses. / H.& E. × 100.

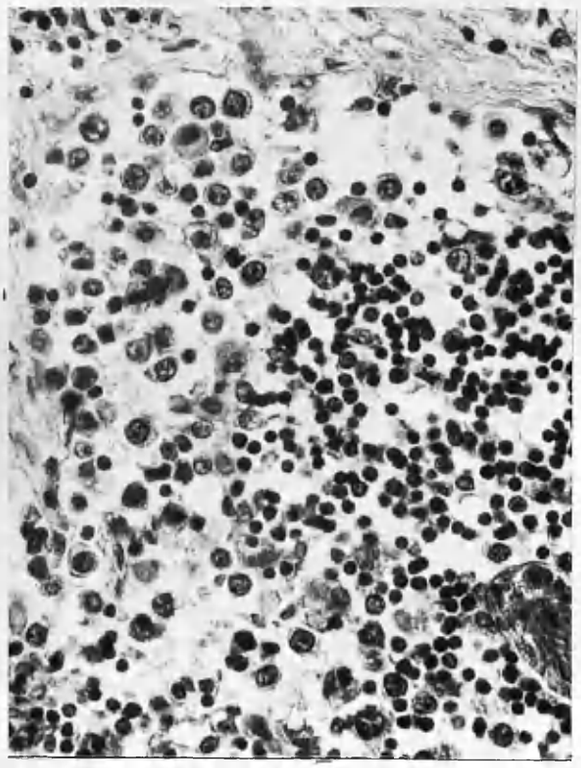


Fig.7. 60. Sinus Catarrh.
Afferent Sinus with numerous monocytoid cells and a few large phagocytes.
H.& E. × 250.

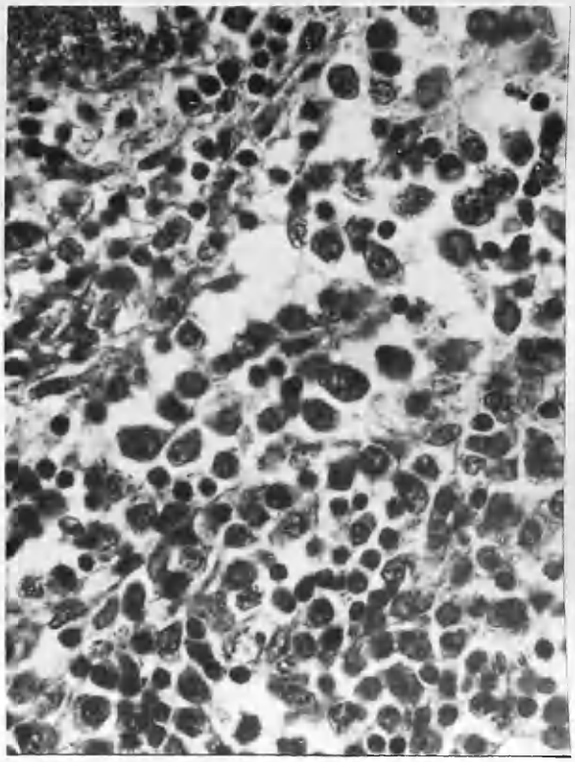


Fig.8. 60. Sinus Catarrh.
Medullary sinus. Swelling of endothelial cells, Some large free cells like those in afferent sinus
H.& E. × 500.

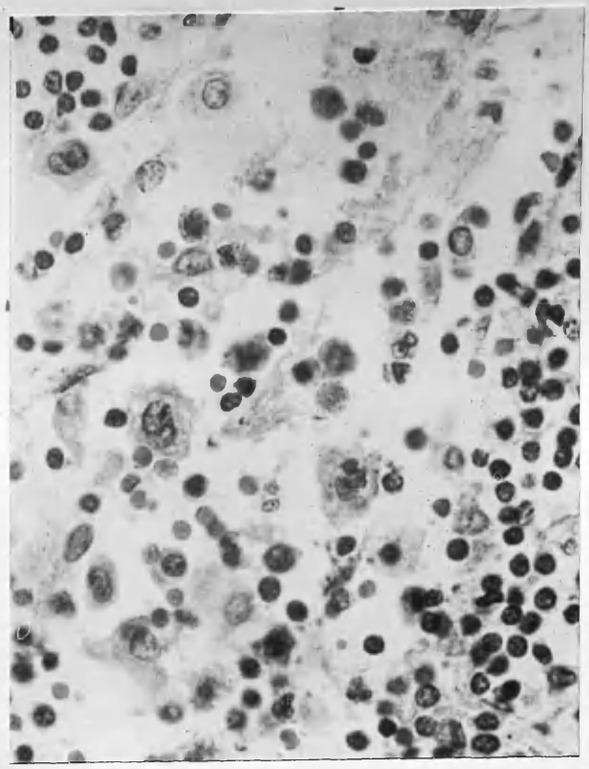


Fig.9. 251. Sinus Catarrh.
Medullary sinus showing large free macrophages and some large cells like those in Fig.8.
H.& E. × 500.

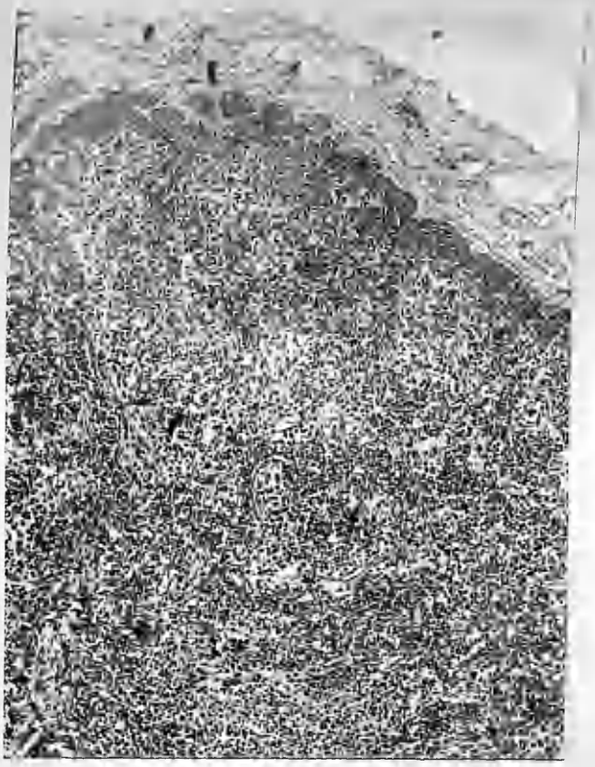


Fig.10.357/38.Haemolymph Gland.
Afferent and medullary sinuses filled with blood.
H.& E. × 150.

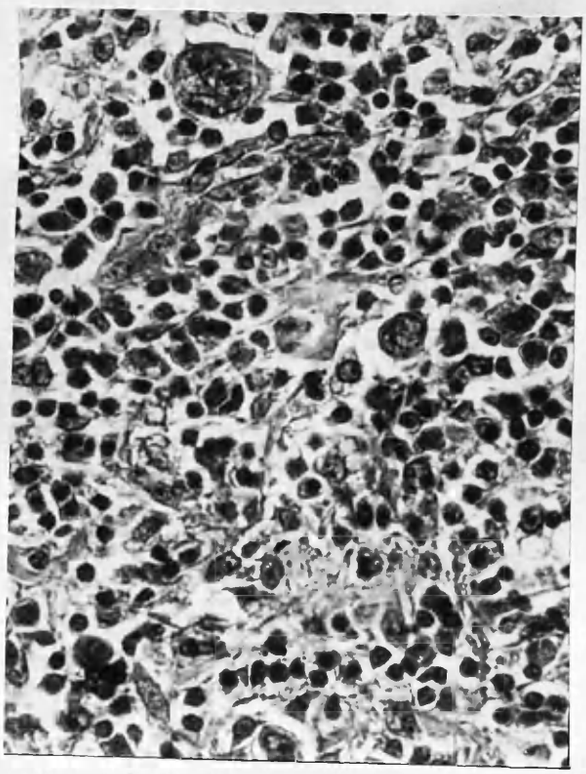


Fig.11.357/38.Haemolymph Gland.
Showing swollen endothelial cells and macrophages.
H.& E. × 500.

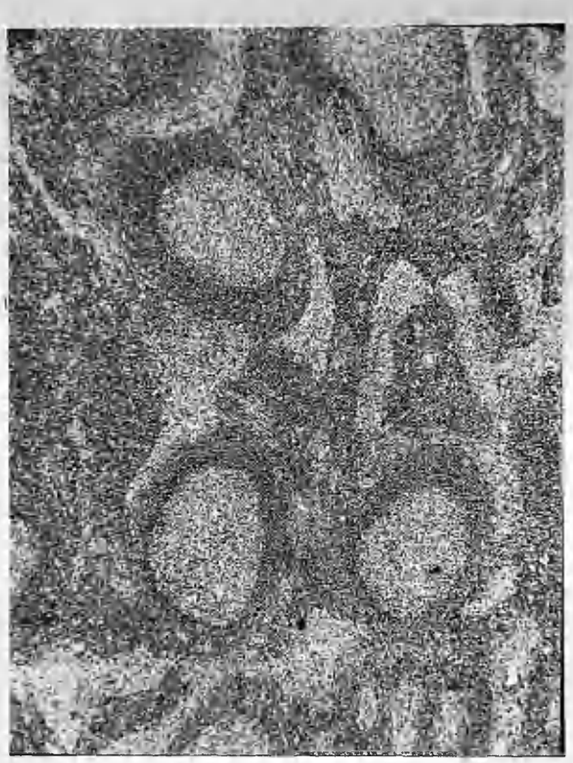


Fig.12.732/35. Reactive Follicular Hyperplasia. Typical large follicles. Sinus catarrh is also present.
H.& E. × 50.

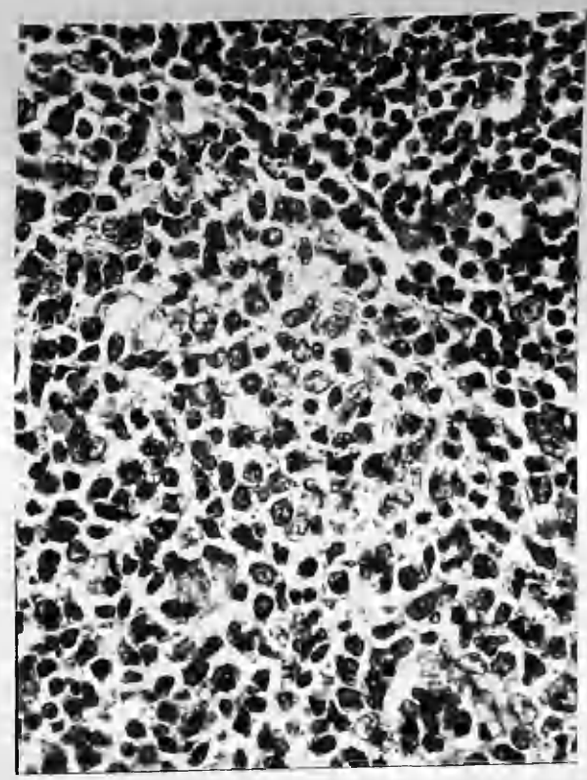


Fig.13. 732/35. Reactive Follicular Hyperplasia.showing pale central portion of follicle to left,lymphocytic rim to right.
H.& E. ×400.

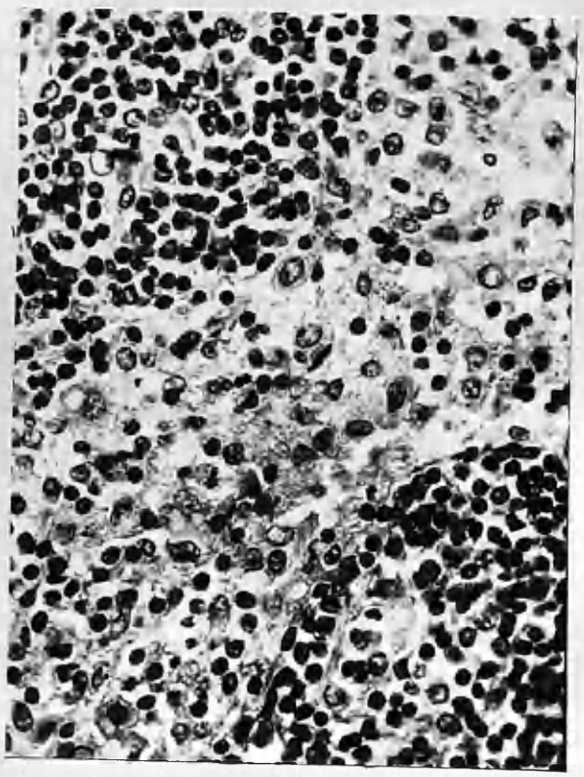


Fig.14.732/35. Reactive Follicular Hyperplasia. Medullary sinus showing solid type of sinus catarrh.
H.& E. × 400.

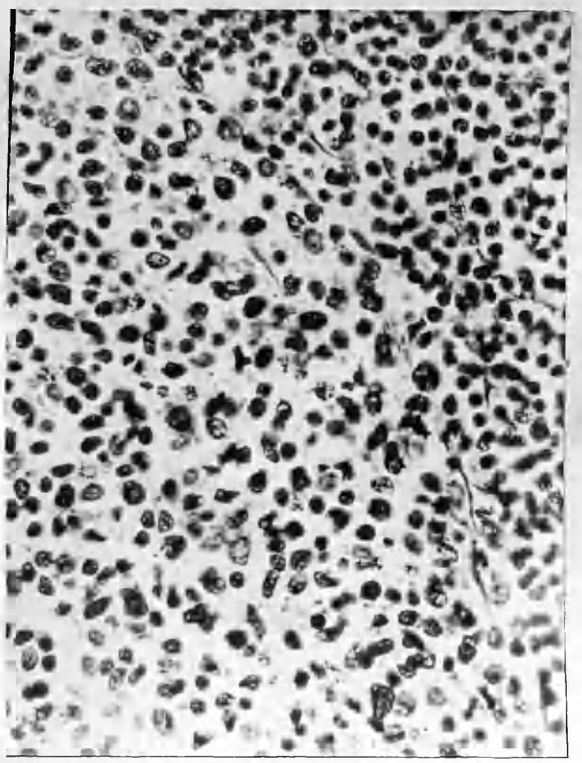


Fig.15.732/35. Reactive Follicular Hyperplasia.Edge of pale centre of follicle showing fine reticulin fibrils.
Silver impregnation.× 400

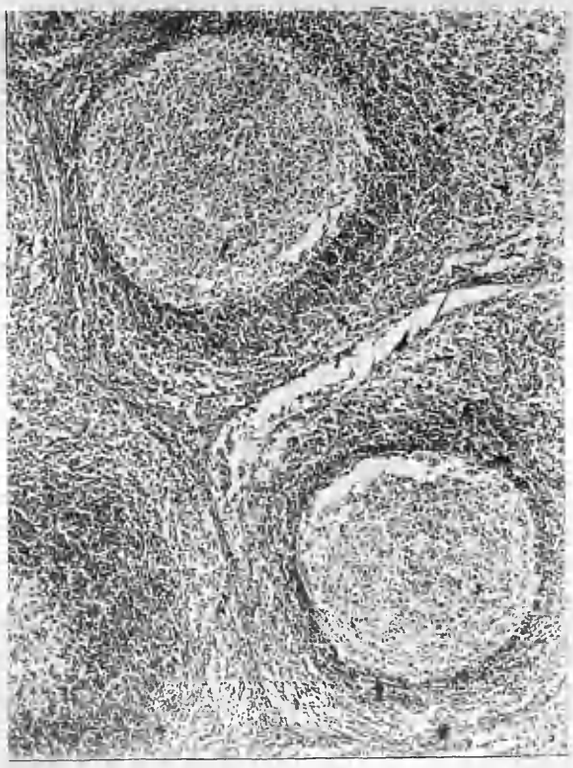


Fig.16.1788/35.Gland showing typical large follicles of reactive follicular hyperplasia. H.& E. × 100.

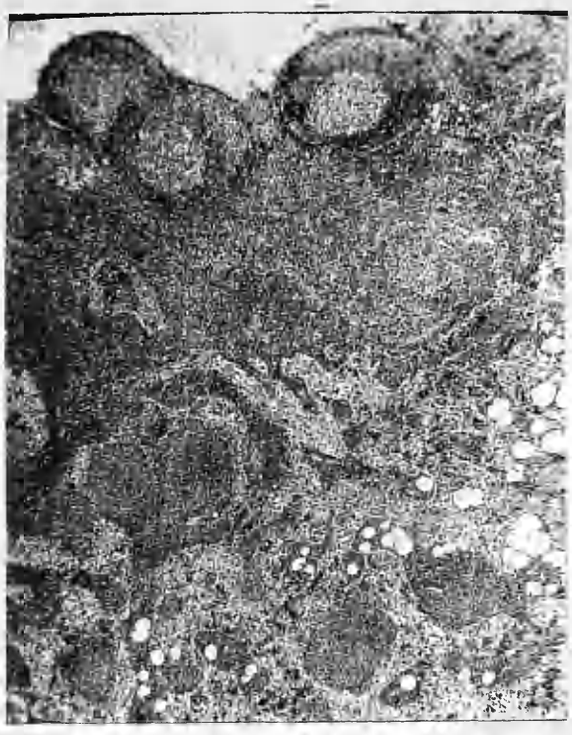


Fig.17. 1788/35.Same gland showing reactive follicular hyperplasia and sinus catarrh. H.& E. × 50.

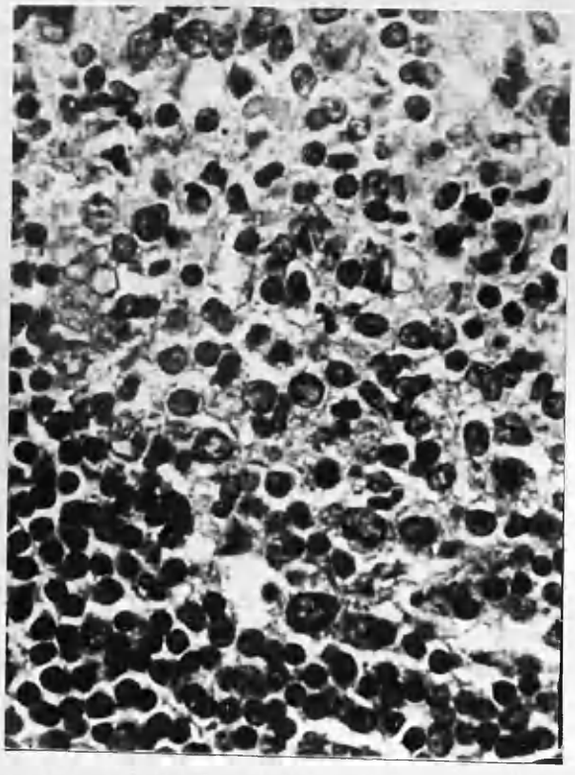


Fig.18. 1788/35. Edge of hyperplastic follicle showing pale centre and dark lymphocytic rim.
H.& E. × 600.

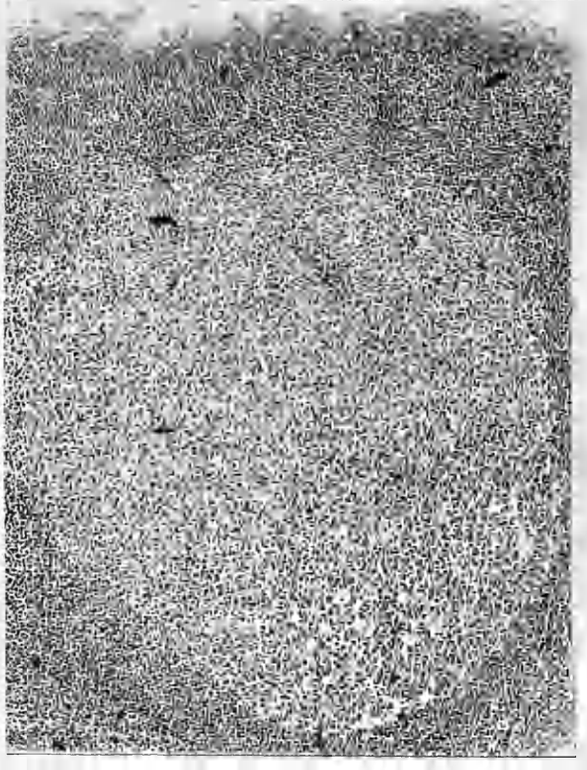


Fig.19. 253. Reactive Follicular Hyperplasia showing typical large follicle.
H.& E. × 100.

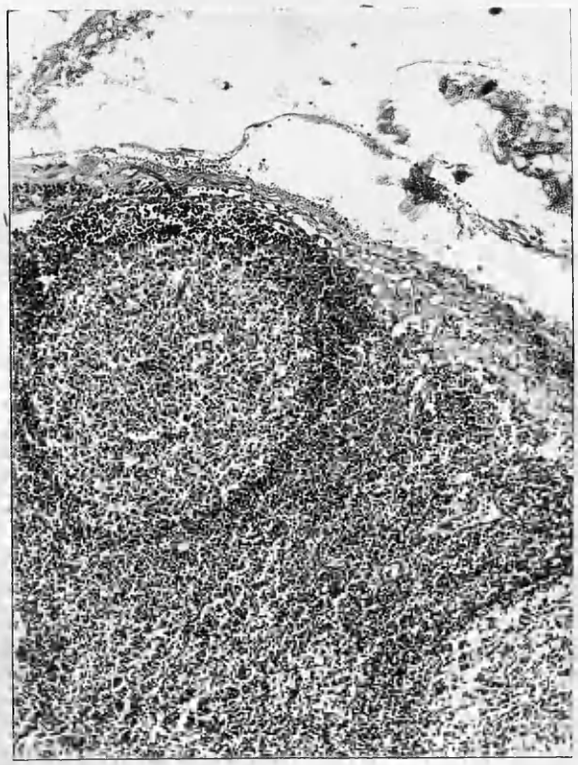


Fig.20.341.Reactive Follicular Hyperplasia showing typical large follicle.
H.& E. × 100.

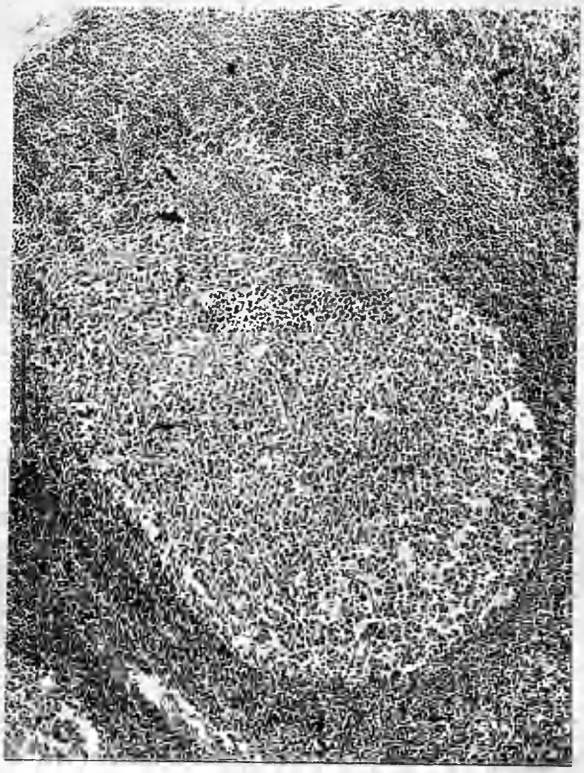


Fig.21. 226. Reactive Follicular hyperplasia showing typical large follicles.
H.& E. × 100.

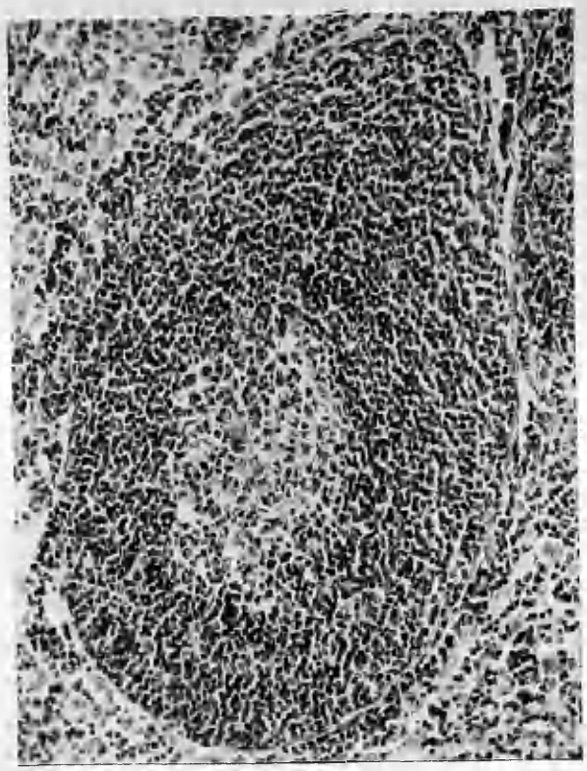


Fig.22.1717.Tuberculous Gland.
A follicle showing reactive follicular hyperplasia.
H.& E.× 150.

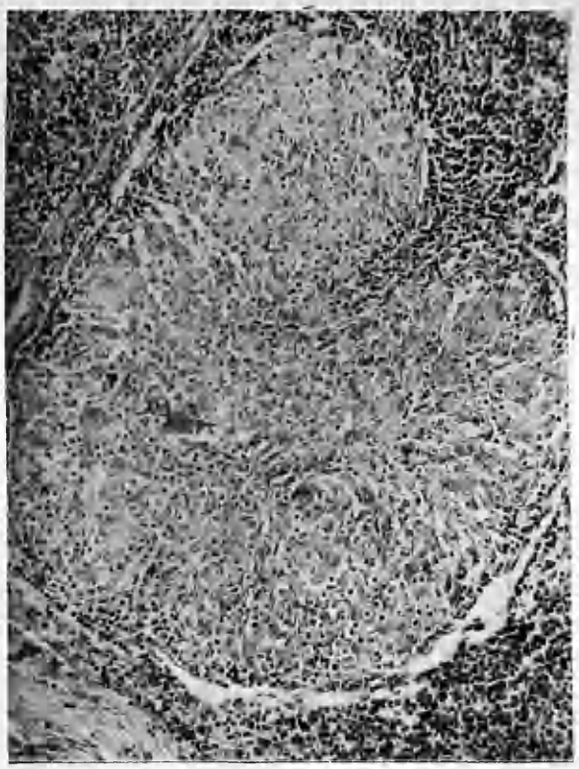


Fig.23.1717.Tuberculous Gland.
Hyperplastic follicle from same gland.composed of epithelioid cell
H.& E.× 150.

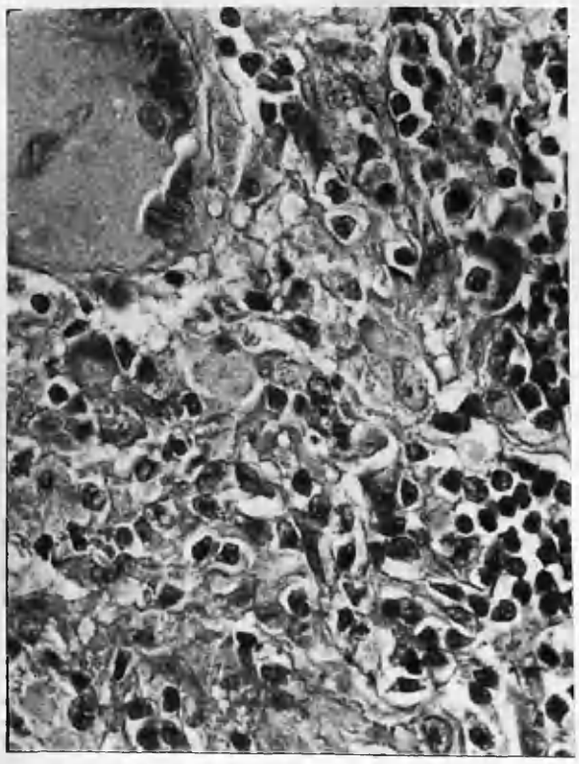


Fig.24.1717.Tuberculous Gland.
Follicle showing epithelioid cells lymphocytes and a tubercle giant cell. H.& E.× 500.

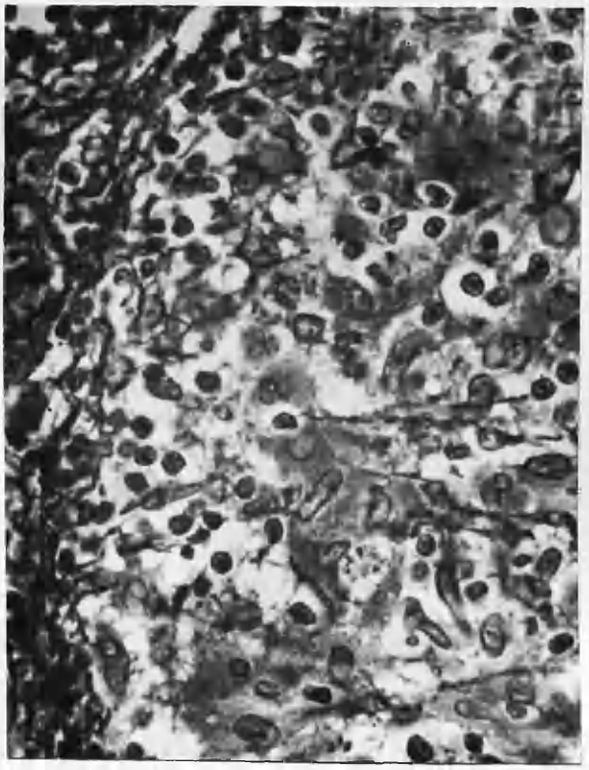


Fig.25. 1717.Tuberculous Gland.
Tubercle follicle showing reticuli around edge and extending into centre.
Silver impregnation.× 500.

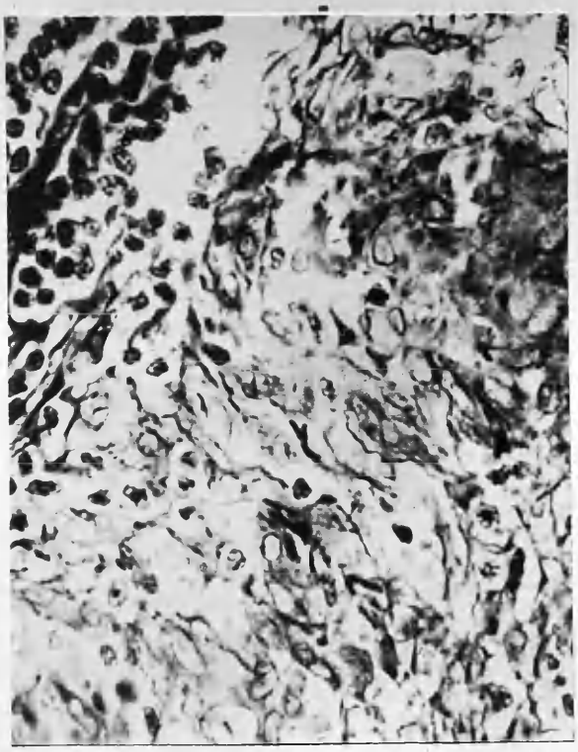


Fig 26. 1717.Tuberculous Gland.
Showing reticulin in centre of tuberculous follicle.
Silver impregnation. × 250.

Fig.27. 890.Tuberculous Gland.
Advanced stage of tuberculous infection.
H.& E.× 50.

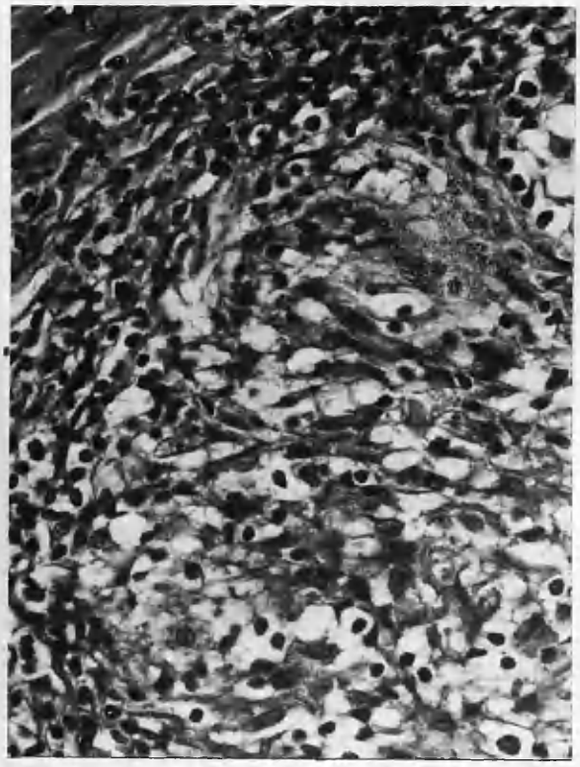


Fig.28. 890.Tuberculous Gland.
Edge of portion of tuberculous tissue,showing stellate cells fusing and extending among peripheral lymphocytes. H.& E.× 500.

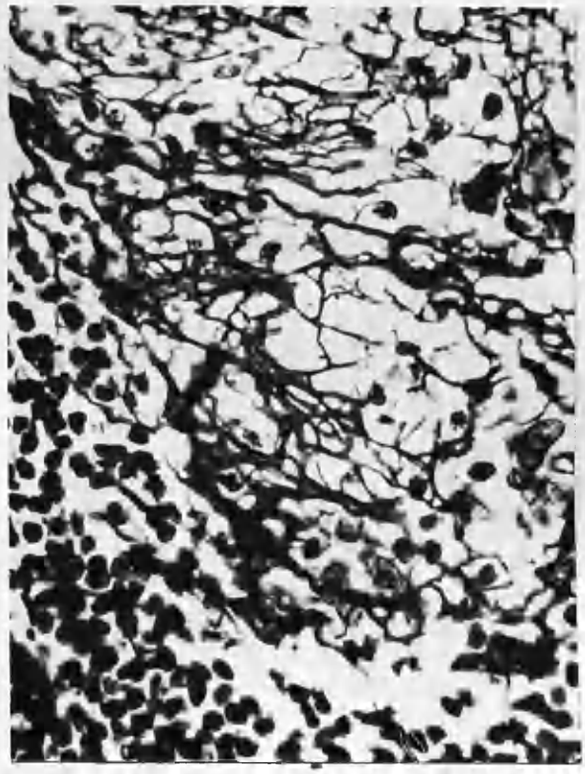


Fig.29. 890.Tuberculous Gland.
Edge of tuberculous tissueto show reticulin which is copious among epithelioid cells scanty among the lymphocytes. H.& E.× 500.

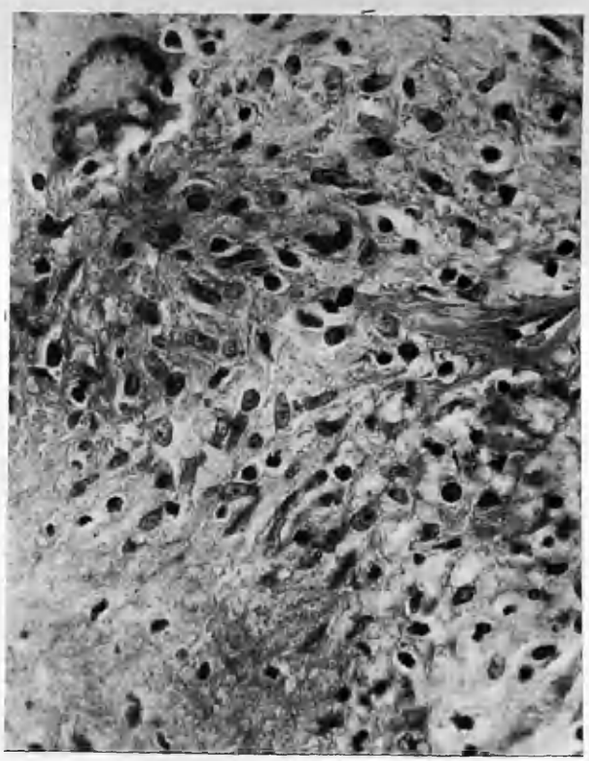


Fig.30. 909.Tuberculous Gland.
Showing fibro-caseous tuberculosis.
H.& E.× 250.

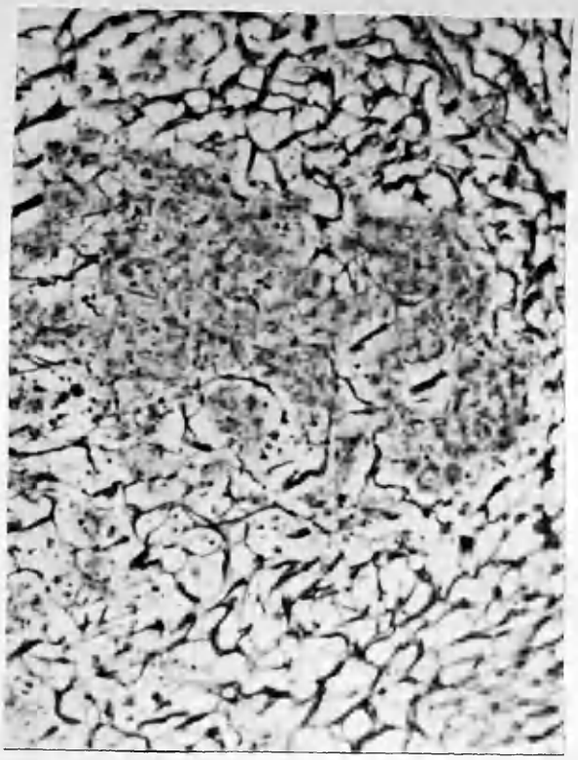


Fig.31. 909.Tuberculous Gland.
Fibro-caseous tissue to show reticulin persisting in caseous area. Silver impregnation.× 250.

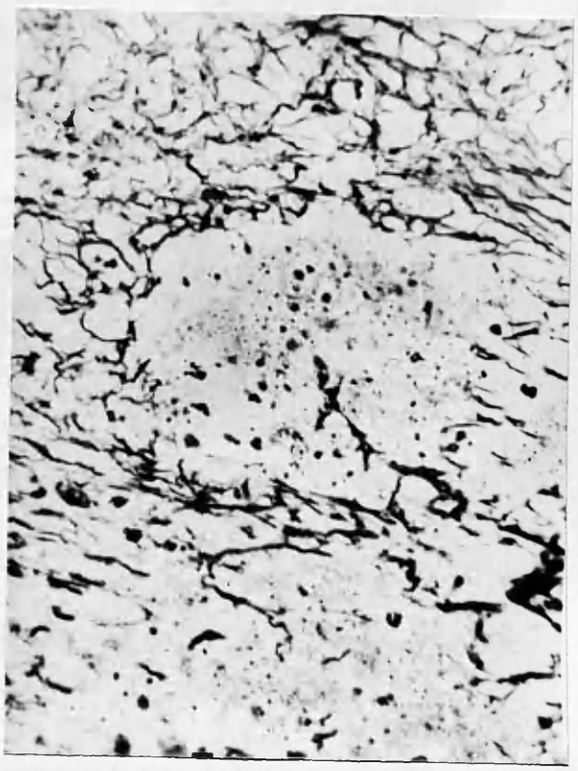


Fig.32. 992. Tuberculous Gland.
Tissue is almost completely caseous.
Silver impregnation.× 250.

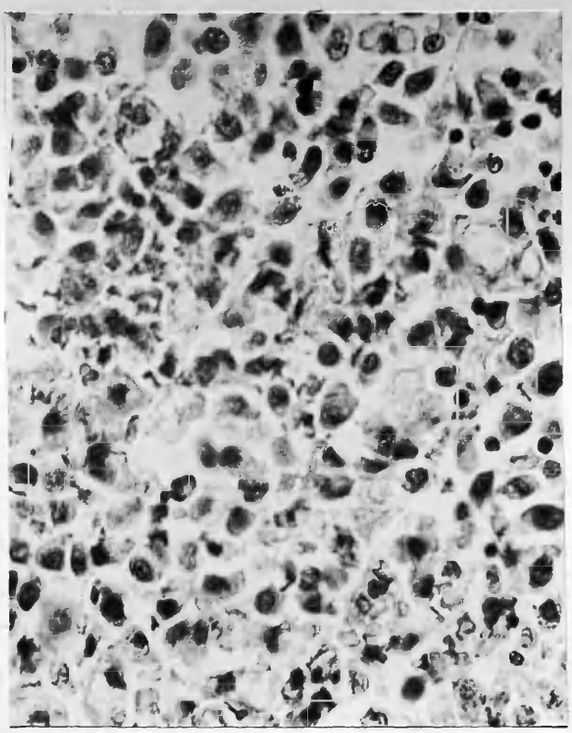


Fig.33.101/39. Acute Reticulosis.
Gland showing uniform cellularity and irregular outline of cells.
H.& E.× 500.

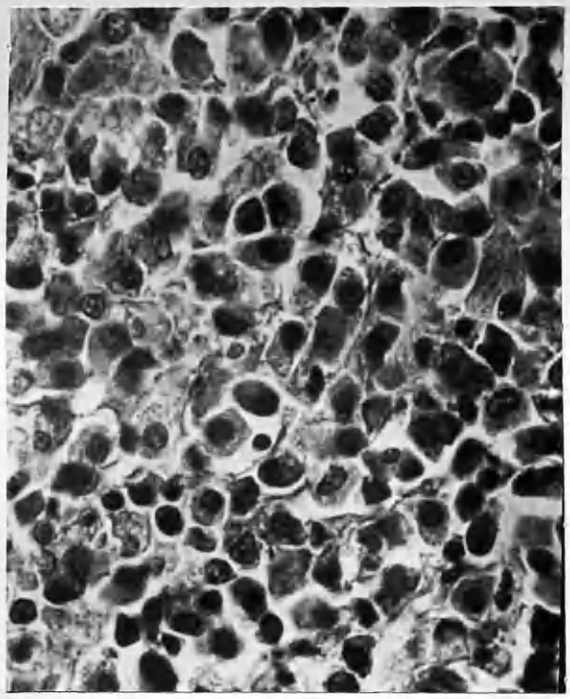


Fig.34. 101/39. Acute Reticulosis.
Similar to fig.33.
H.& E.× 600.

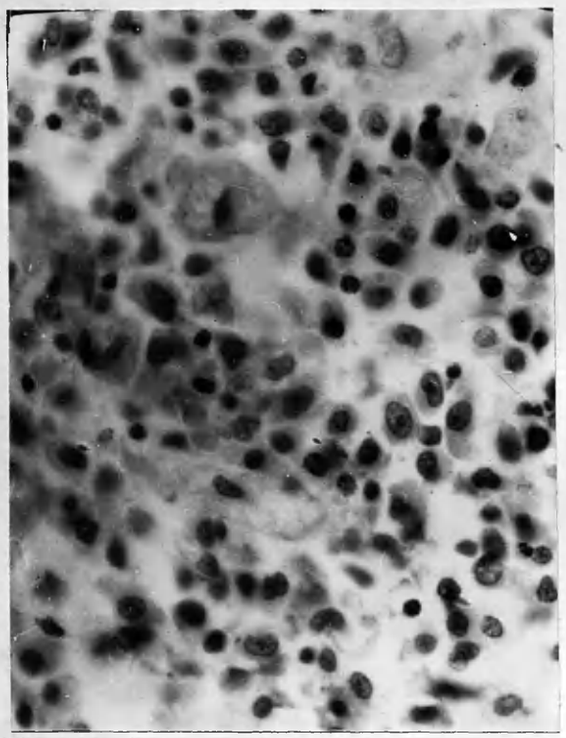


Fig.35. 101/39. Acute Reticulosis.
Gland showing an actively phagocytic macrophage.
H.& E.× 300.

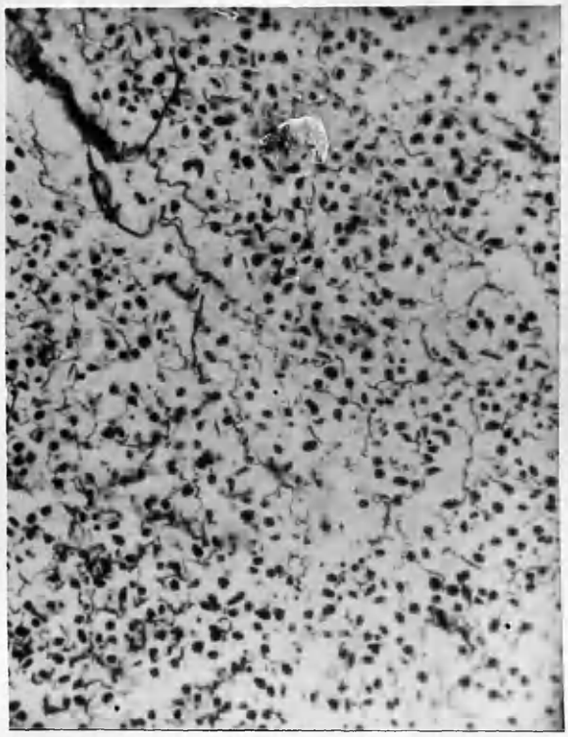


Fig.36. 101/39, Acute Reticulosis.
Gland showing fine, scanty reticulin fibrils.
Silver impregnation.× 150.

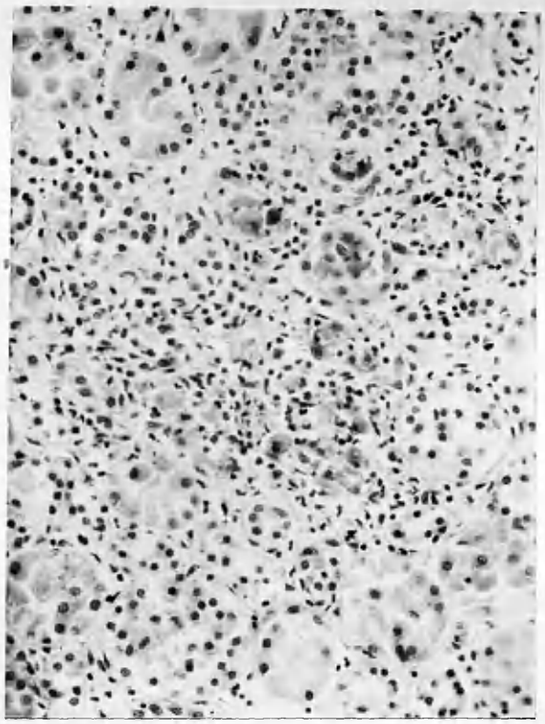


Fig.37. 101/39. Acute Reticulosis.
Kidney extensively infiltrated
with type cells.
H.& E. × 150

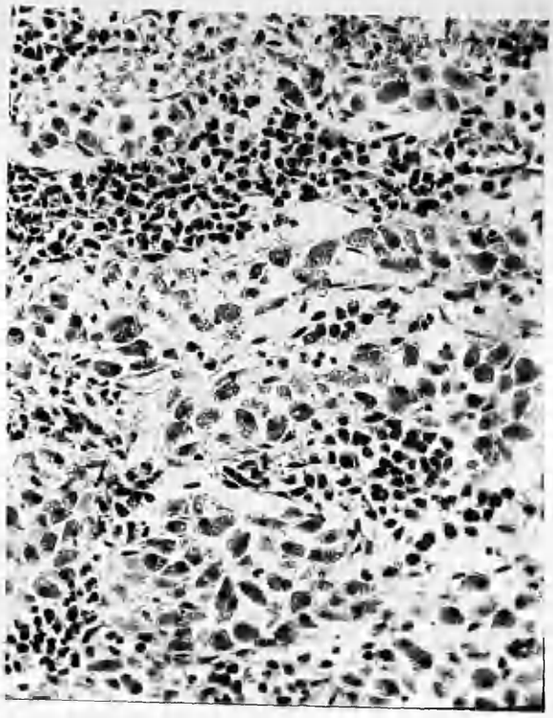


Fig.38. 101/39. Acute Reticulosis.
Suprarenal gland showing areas
of ? infiltration.
H.& E. × 250.

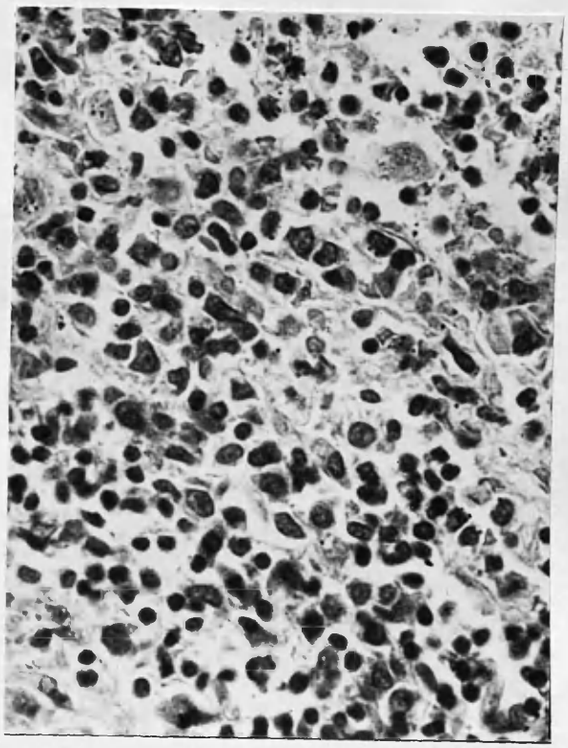


Fig.39. 101/39. Acute Reticulosis.
Splenic pulp filled with type cell
also a few macrophages.
H.& E. × 500.

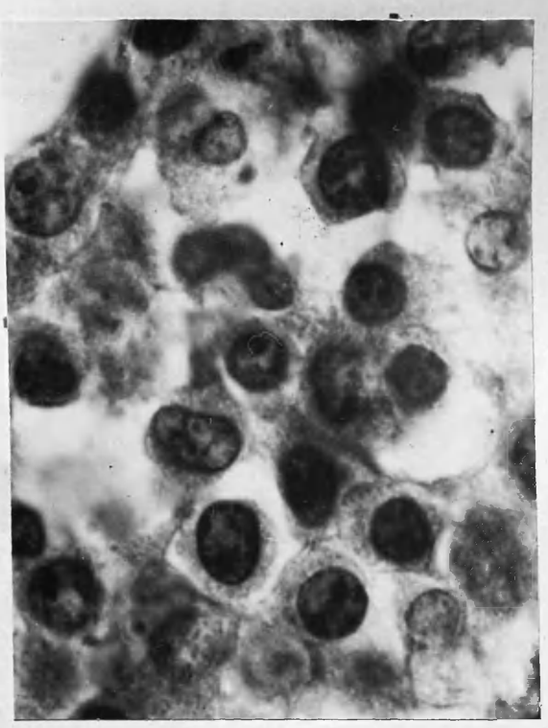


Fig.40. 101/39. Acute Reticulosis. Gland showing type cells, partly syncytial. A macrophage is present towards upper edge. H.& E.× 1000.

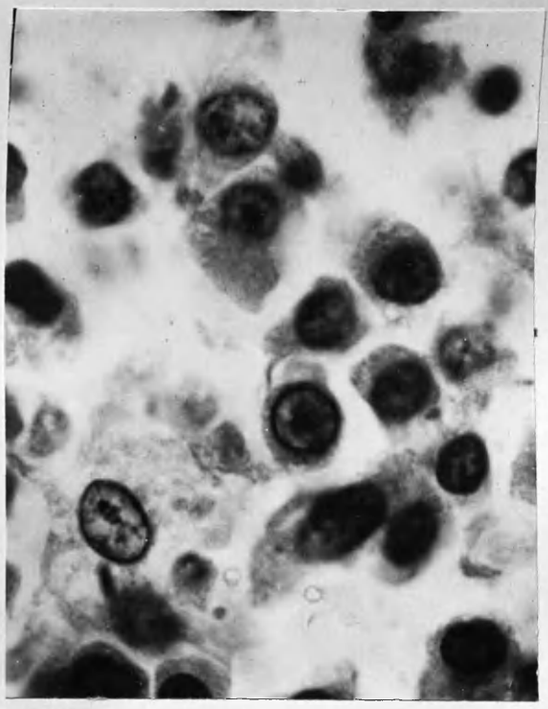


Fig.41.101/39.Acute Reticulosis. Bone marrow showing type cells with distinct nuclear rim and nucleolus. H.& E.× 1000.

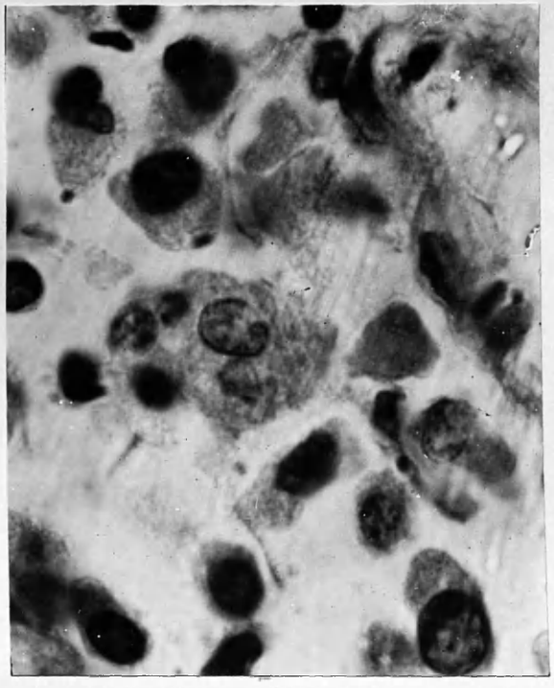


Fig.42.101/39. Acute Reticulosis. Part of Malpighian Body.showing reticulum cells and one macrophage. H.& E.× 1000.

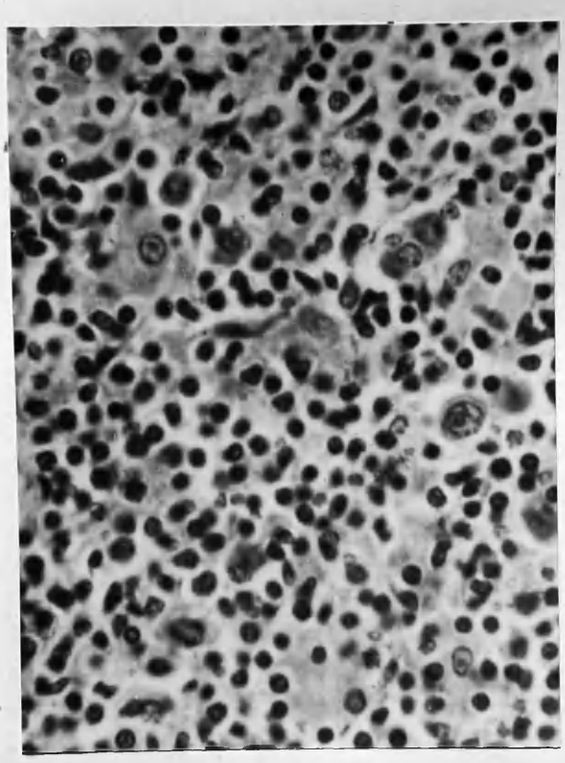


Fig.43.19/46.Acute Reticulosis.
Gland showing hyperplastic reticulim cells.
H.& E.× 500.

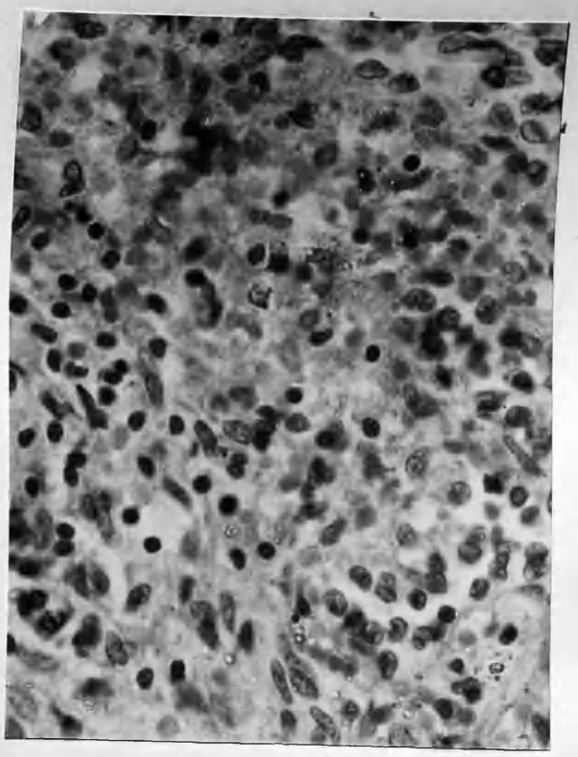


Fig.44.19/46. Acute Reticulosis.
Splenic pulp which is relatively avascular due to hyperplasia of reticulum cells. H.& E.× 500.

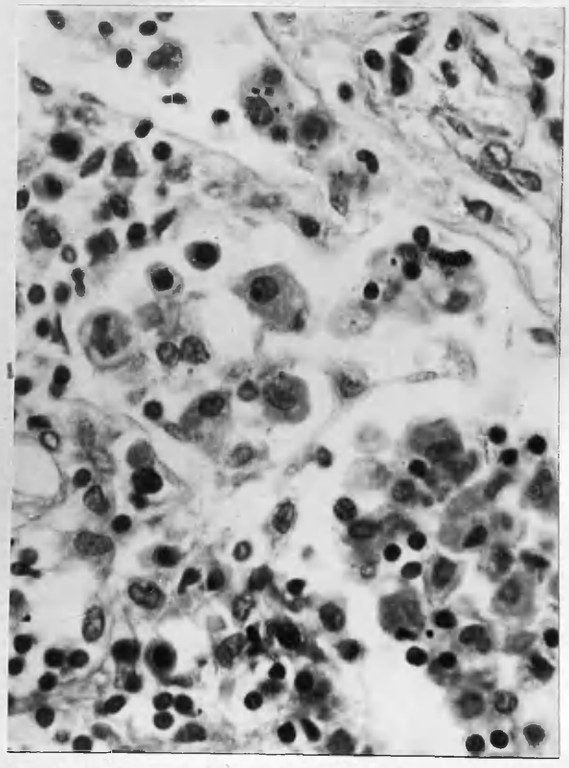


Fig.45.19/46. Acute Reticulosis.
Lymphatic sinus showing hyperplasia of reticulum cells also large free phagocytic cells.
H.& E. × 500.

Fig.46.19/46. Acute Reticulosis.
Lymphatic Gland to show reticulin.
Silver impregnation. × 500.

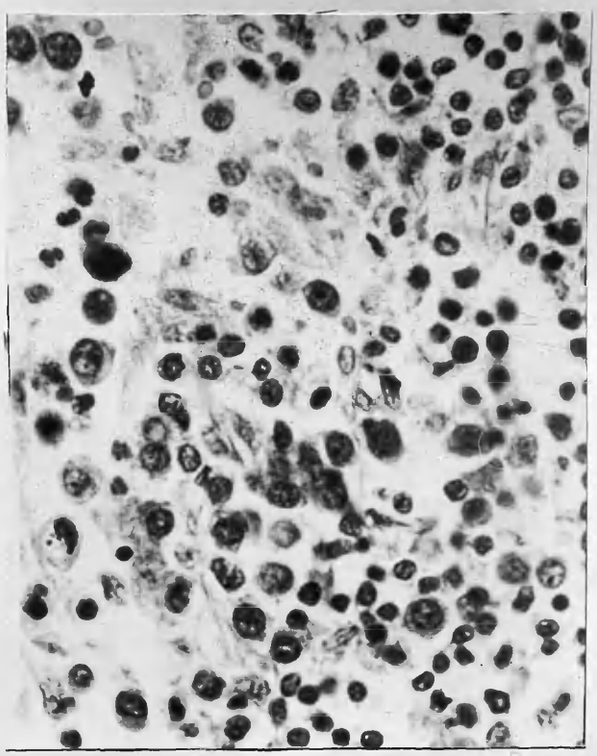


Fig.47.125. Acute Reticulosis.
Gland showing numerous large mononuclear cells,mostly free.
H.& E .× 500.

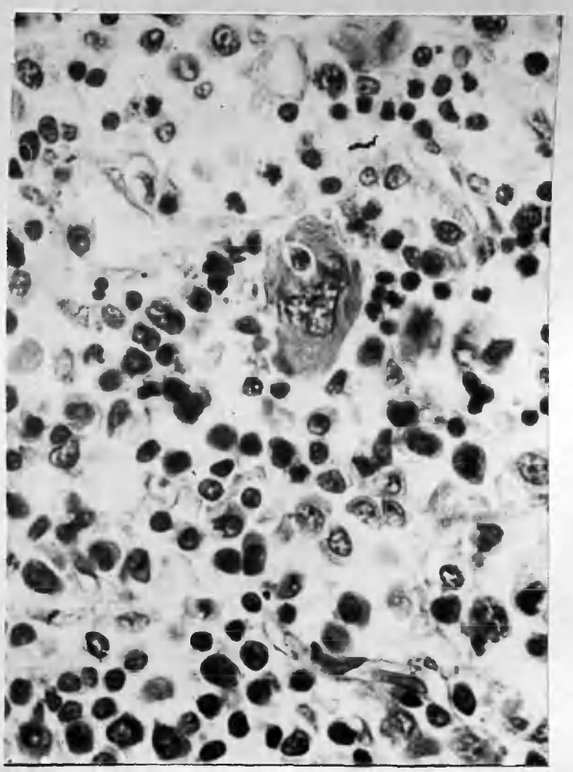


Fig.48. 125. Acute Reticulosis.
Gland showing large mononuclear cells & one very large macrophage.
H.& E. × 500.

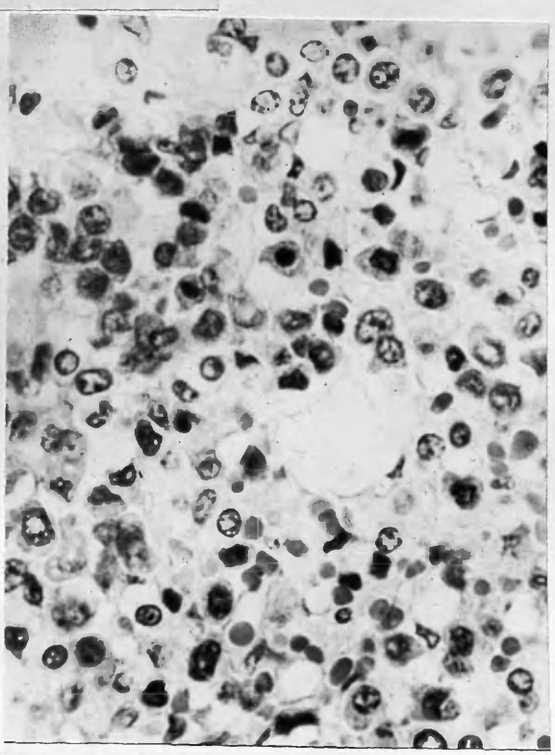


Fig.49. 125. Acute Reticulosis.
Bone marrow showing mononuclear cells.
H.& E. ×500.

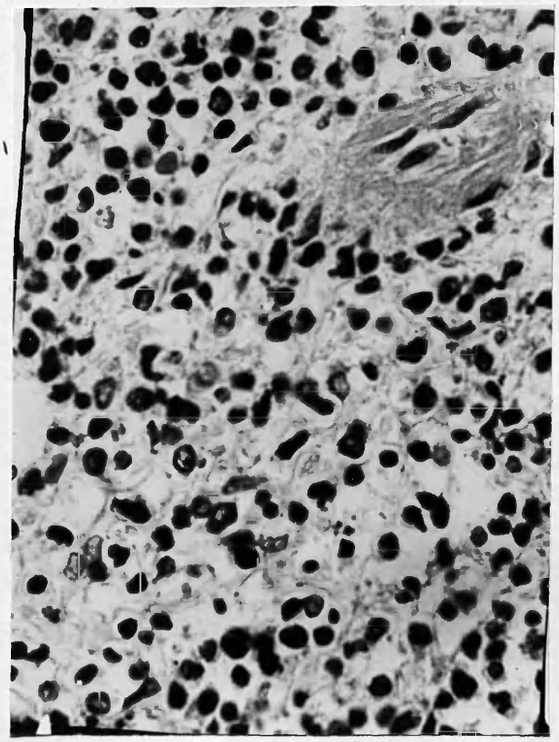


Fig.50.125. Acute Reticulosis.
Spleen showing lack of definition of Malpighian body, with hyperplasia of reticulum cells.
H.& E.× 500.

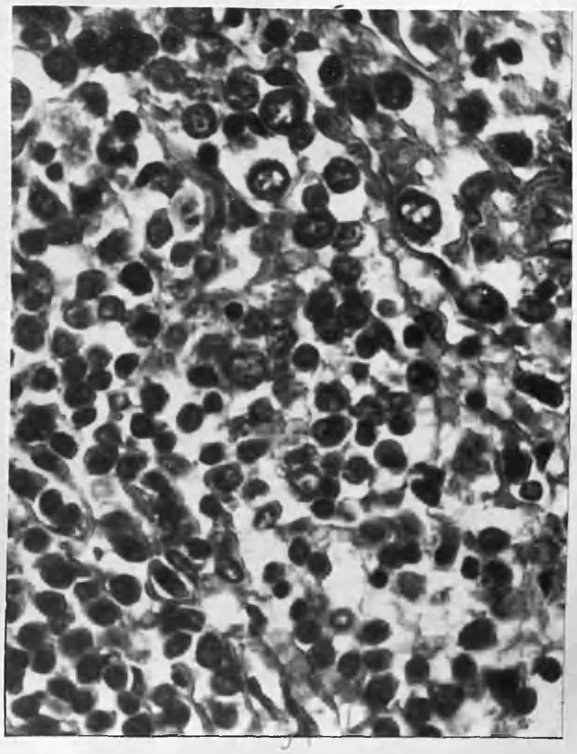


Fig.51.125.Acute Reticulosis.
Splenic pulp showing hyperplastic reticulum cells, some large.
H.& E.× 500.

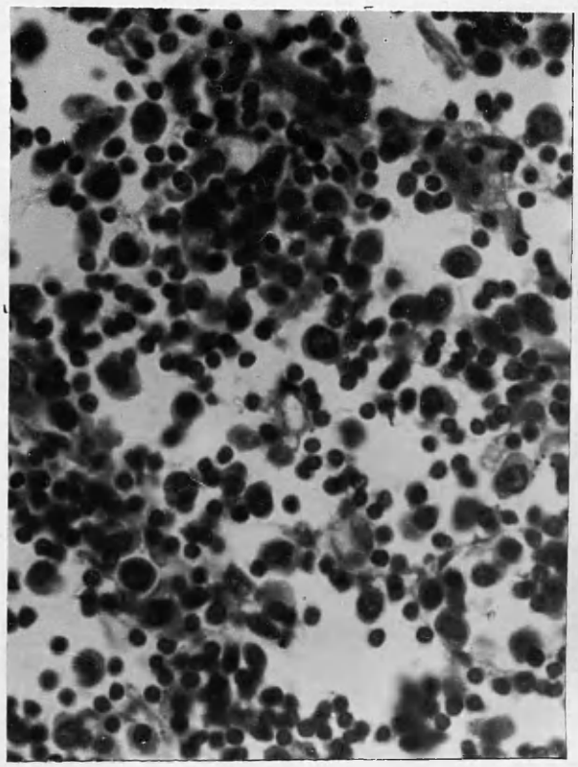


Fig.52.264. Acute Reticulosis.
Gland showing numerous lafge free cells. Some hyperplasia of fixed reticulum cells.
H.& E. × 500.

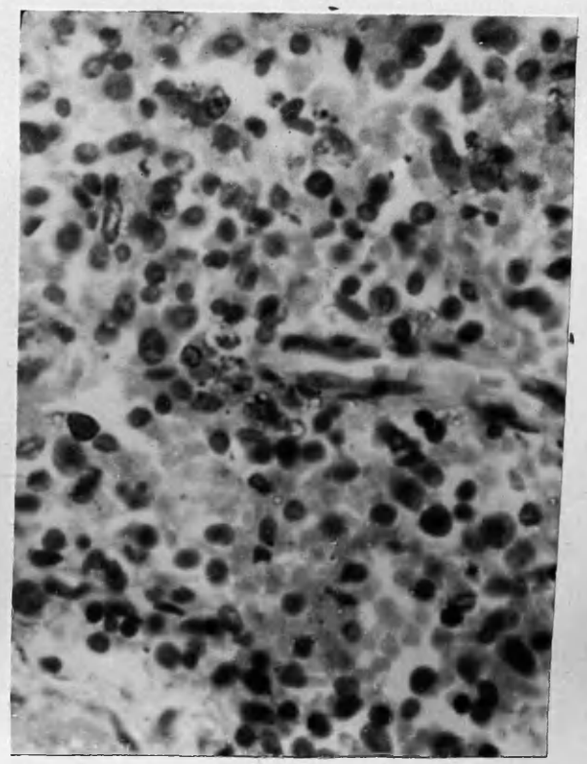


Fig153.264. Acute Reticulosis.
Splenic pulp showing hyperplasia of reticulum cells.
H.& E. × 500.

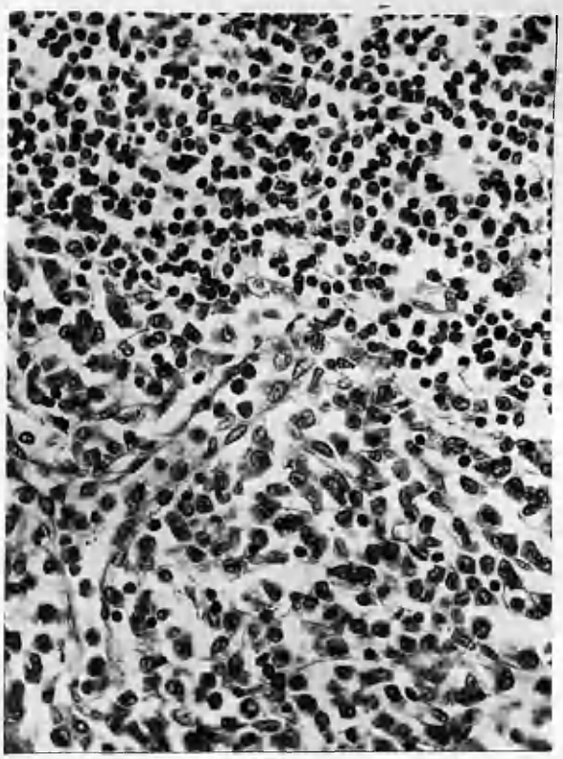


Fig.54.16512.Monocytic Leukaemia.
Gland showing hyperplastic reticulum cells invading a focus of lymphocytes.
H.& E.× 400.

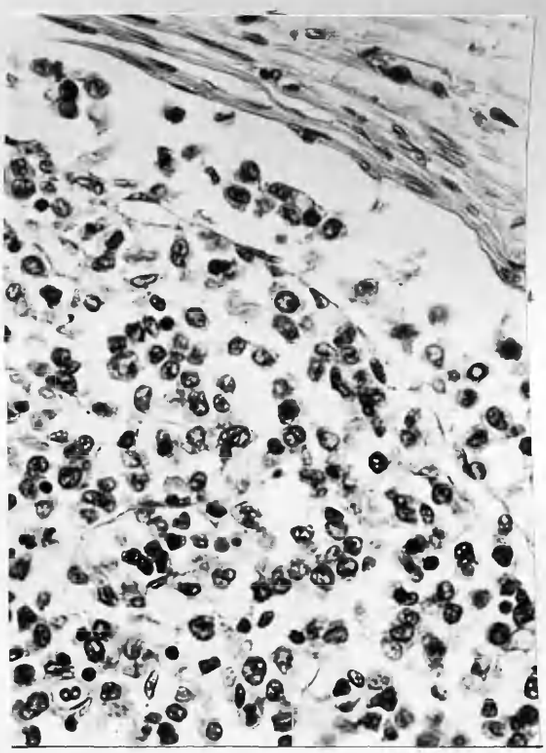


Fig.55.16512.Monocytic Leukaemia.
Gland. Afferent sinus showing monocytes.Lymphocytes of cortex largely replaced by monocytoid cells. H.& E.× 500.

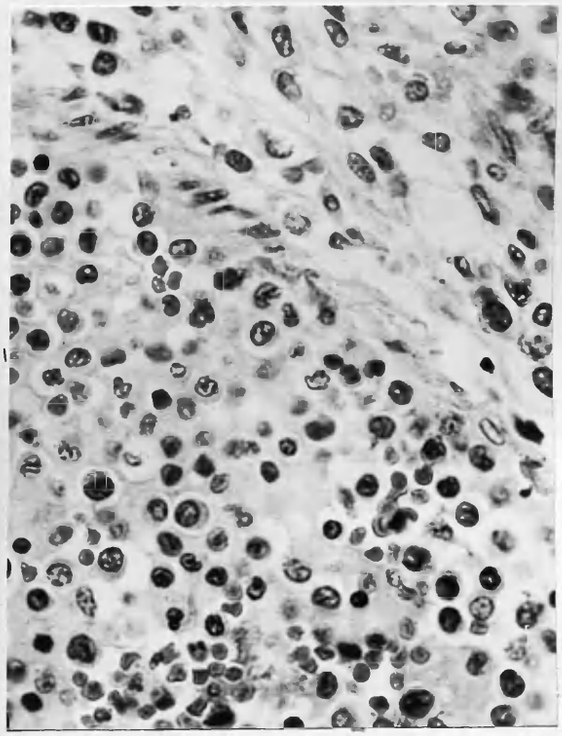


Fig.56.16512.Monocytic Leukaemia.
Blood vessel in capsule of gland containing monocytes.
H.& E.× 500.

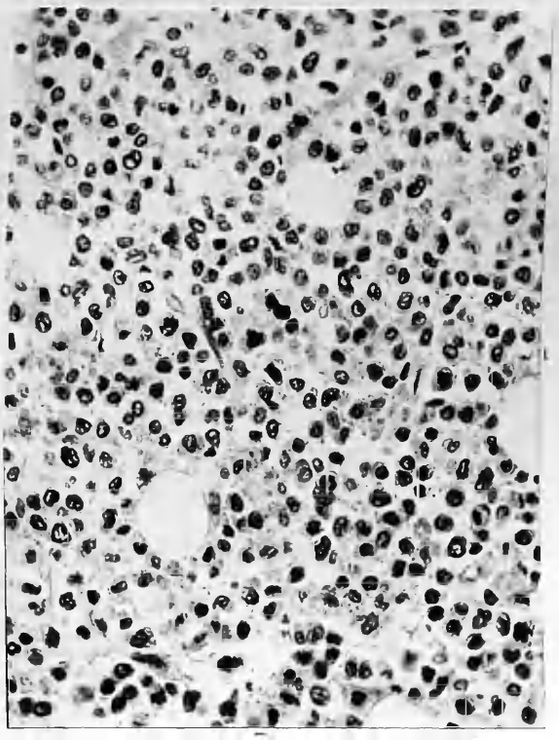


Fig.57.16512.Monocytic Leukaemia.
Bone marrow showing numerous monocytes.
H.& E.× 400.

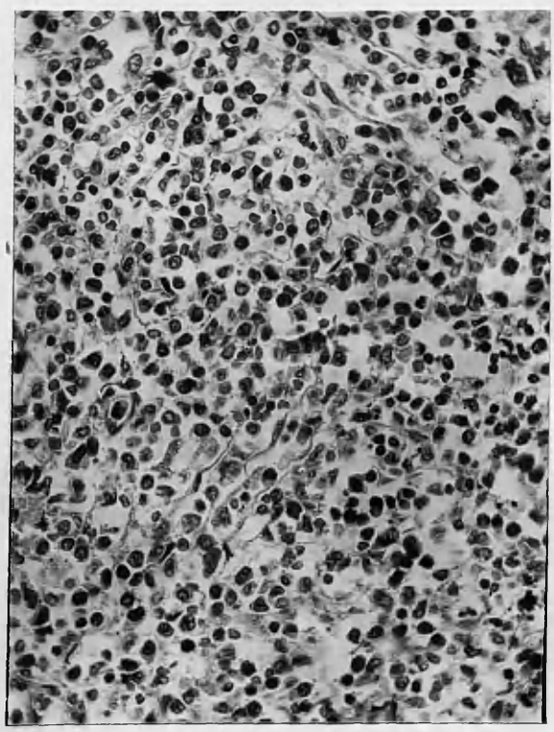


Fig.58.16512.Monocytic Leukaemia. Spleen.Hyperplastic reticulum cells Many monocytes are free in the sinuses.Sinus endothelium is not swollen. H.& E. × 400.

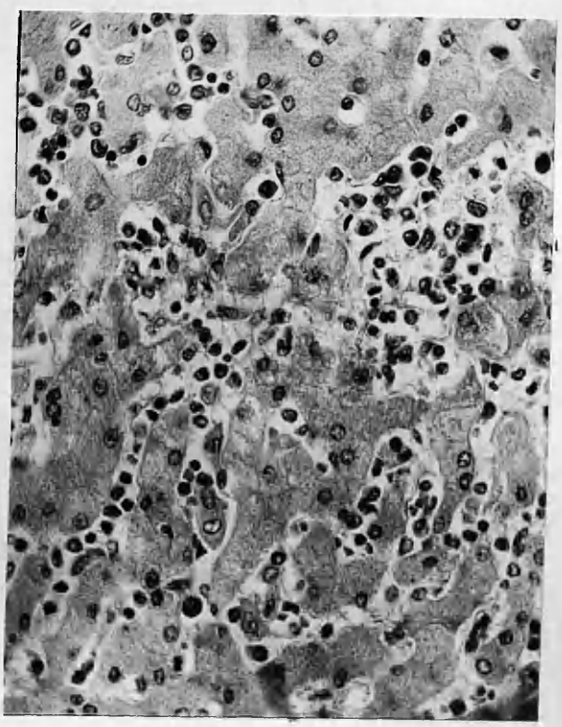


Fig.59.16512.Monocytic Leukaemia. Liver infiltrated with monocytic cells.
H.& E. × 400.

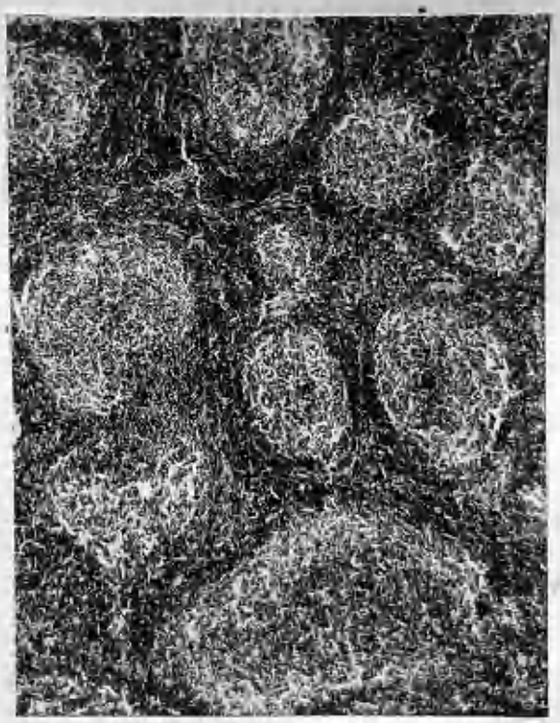


Fig.60.1950.Giant Follicular Hyperplasia.Appearance similar to reactive follicular hyperplasia.
H.& E.× 150.

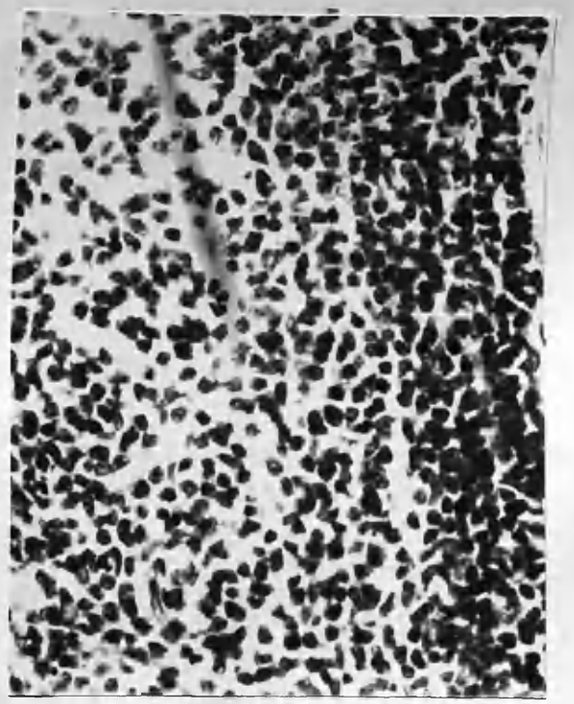


Fig.60a.1950. Giant Follicular Hyperplasia.Loose centre of follicle to left,condensed rim to right.
H.& E.× 400.

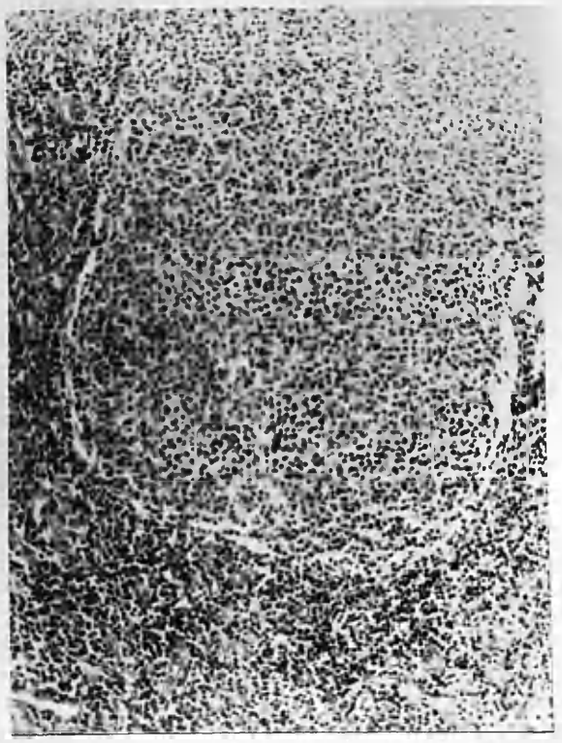


Fig.61.1752/45.Giant Follicular Hyperplasia. Showing one large follicle.
H.& E.× 150.

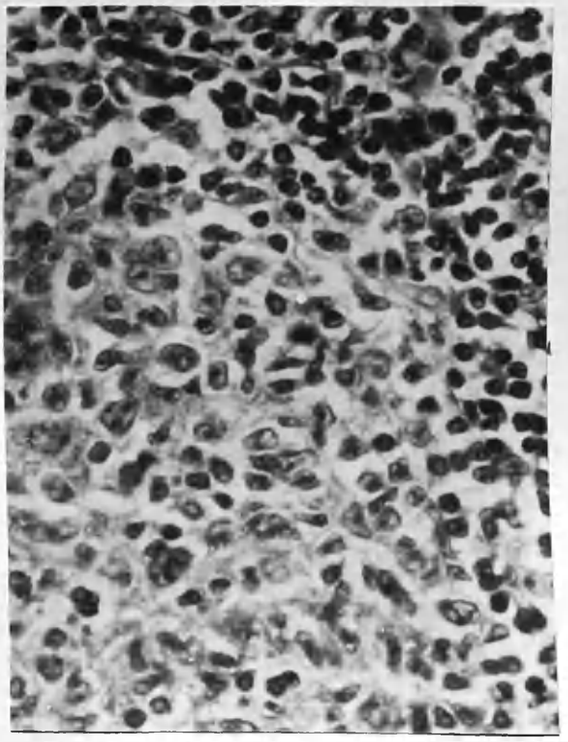


Fig.62.1752/45. Giant Follicular Hyperplasia.Edge of follicle showing hyperplastic reticulum cells and surrounding lymphocytes.
H.& E.× 500.

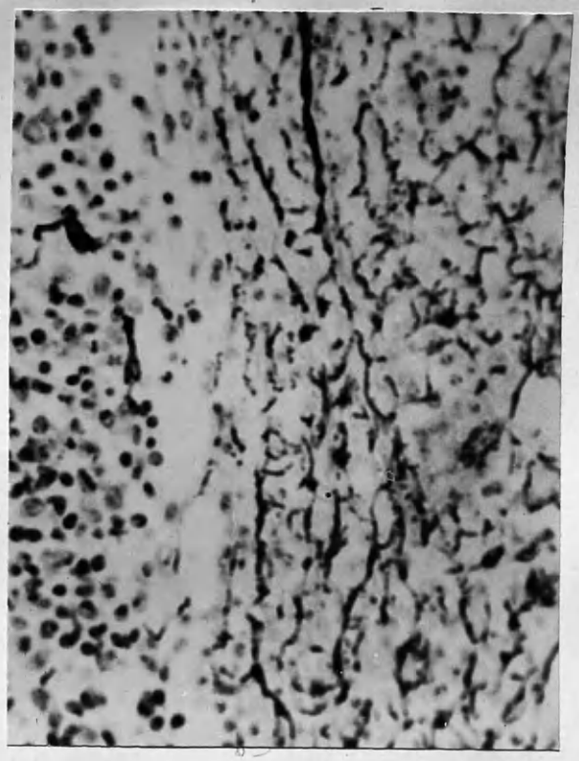


Fig.63.1752/45. Giant Follicular Hyperplasia.Scanty reticulin at periphery of follicle,absent in centre.
Silver impregnation.× 500.

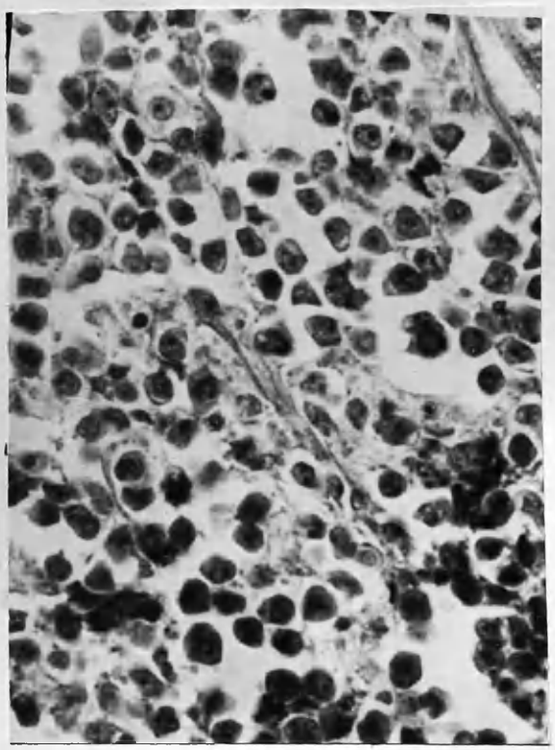


Fig.64.600/46. Giant Follicular Hyperplasia. Gland showing disorderly hyperplasia of reticulum cells.
H.& E. × 500.

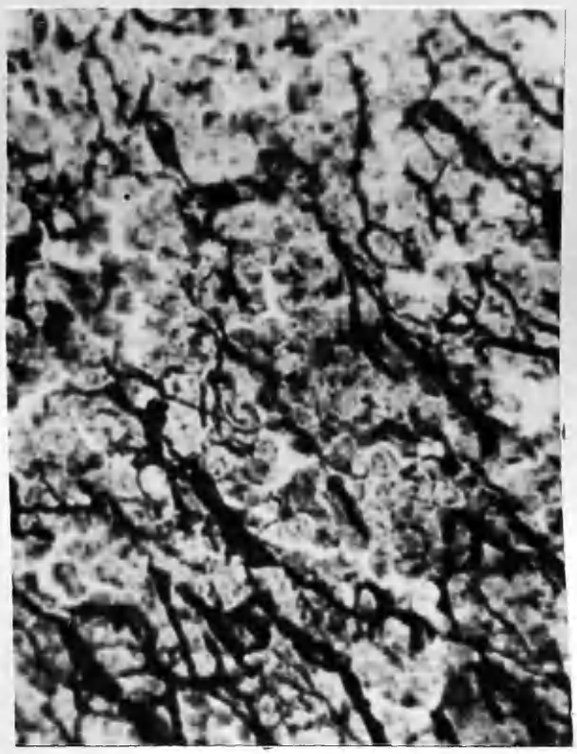


Fig.65.600/46.Giant Follicular Hyperplasia. Irregular,coarse reticulin fibrils.
Silver impregnation.× 500.

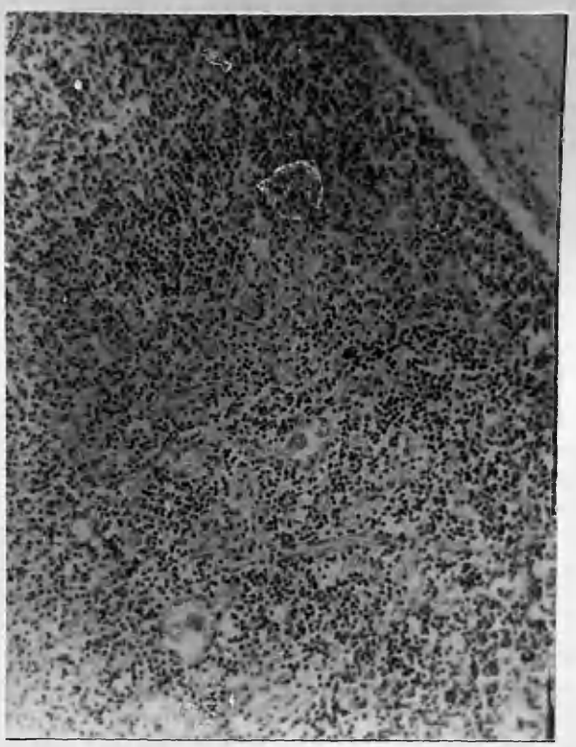


Fig.66.308/37.Chronic Reticulosis.
Gland showing cellularity with fairly numerous large cells projecting into spaces.
H.& E.× 100.

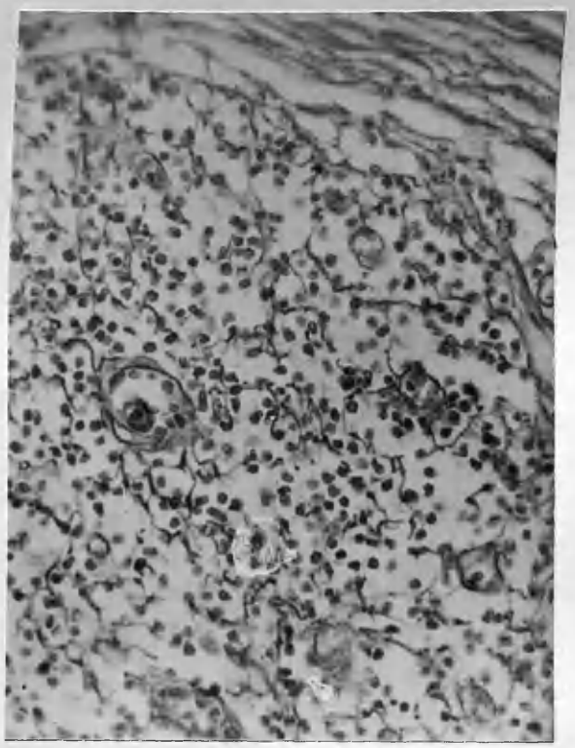


Fig.67.308/37.Chronic Reticulosis.
Gland showing fine reticulin.
Silver impregnation.× 400.

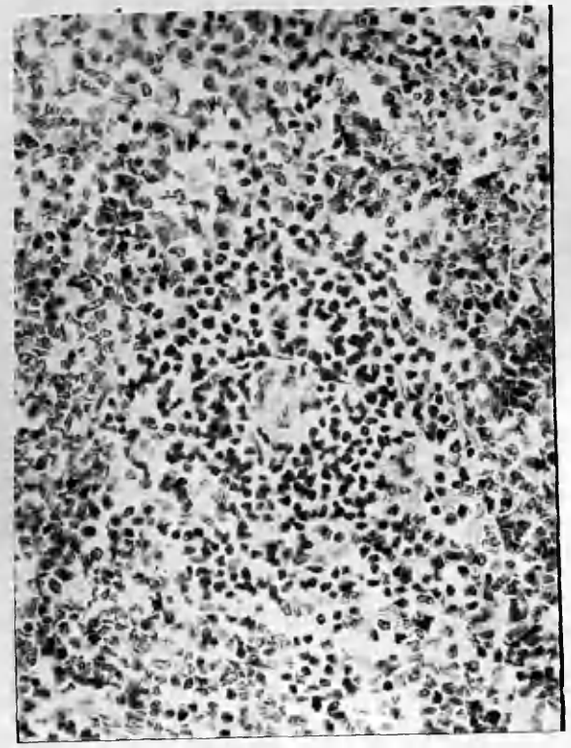


Fig.68.308/37.Chronic Reticulosis.
Spleen. Malpighian body is indistinct from pulp.
H.& E.× 400.

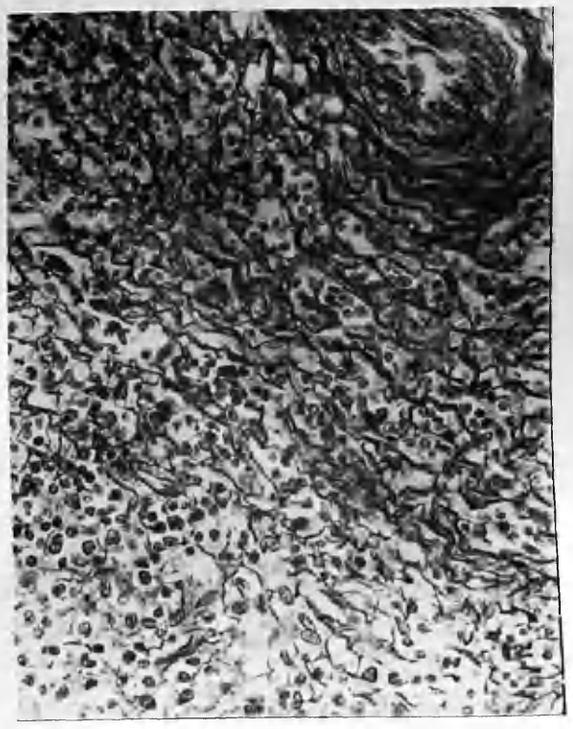


Fig.69.308/37.Chronic Reticulosis.
Spleen to show copious reticulin in Malpighian body.
Silver impregnation.× 400.

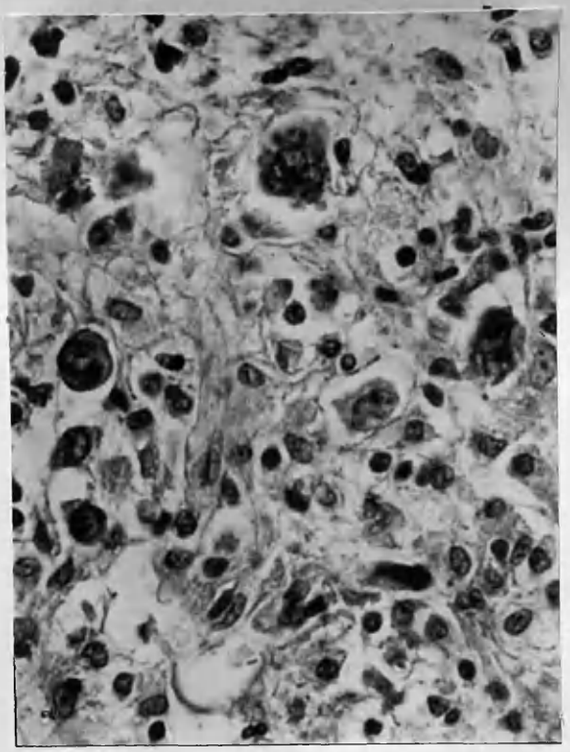


Fig.70.103/39.Chronic Reticulosis.
Gland showing giant cells and
hyperplastic reticulum cells.
H.& E.× 500.

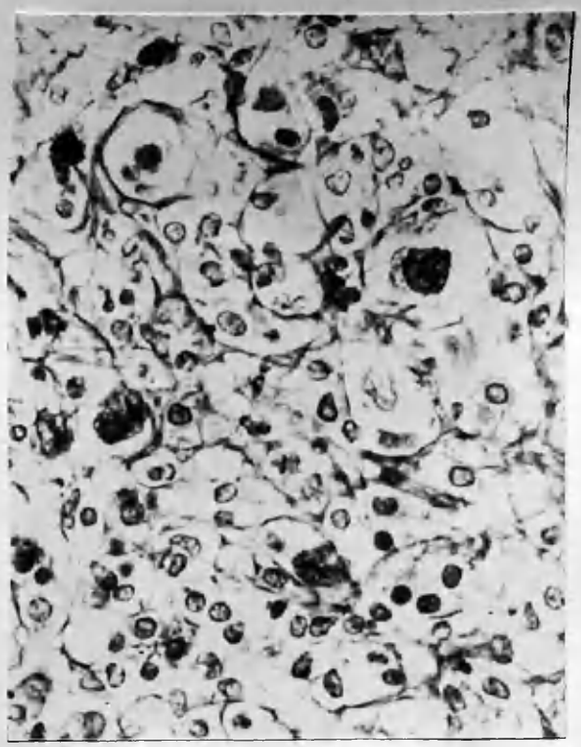


Fig.71.103/39.Chronic Reticulosis.
Gland showing fine interlacing
reticulin fibrils.
Silver impregnation.× 500.

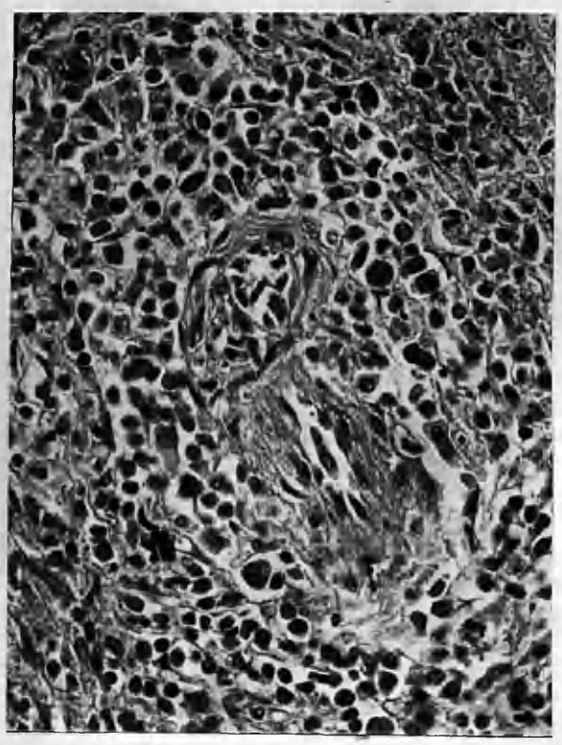


Fig.72.103/39.Chronic Reticulosis.
Spleen with hyperplasia of
reticulum cells in Malpighian
body.
H.& E.X 300.

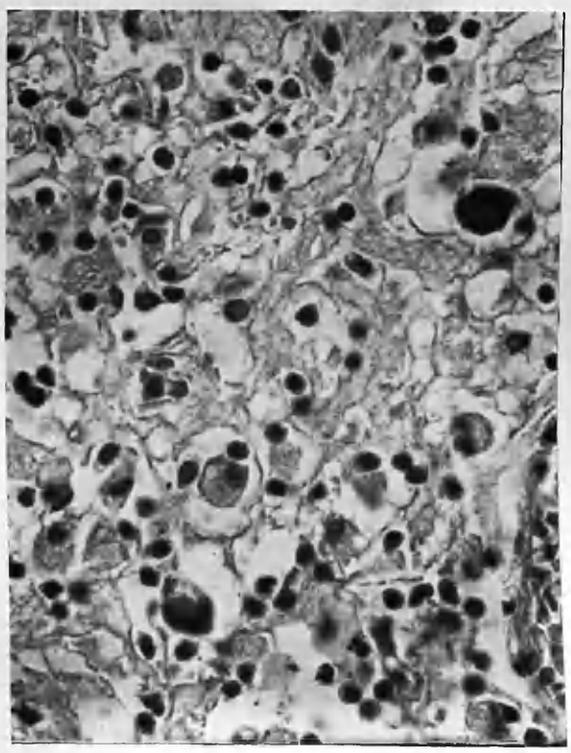


Fig.73.103/39.Chronic Reticulosis.
Bone marrow to show fibrillary
tissue and large cells.
H.& E. x500.

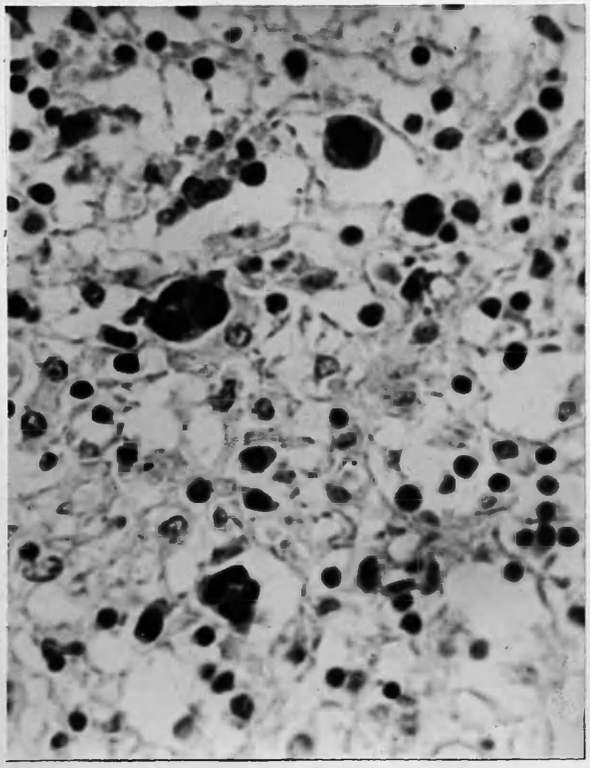


Fig.74.108/39.Chronic Reticulosis.
Gland showing fibrillary tissue
and giant cells.
H.& E.× 500.

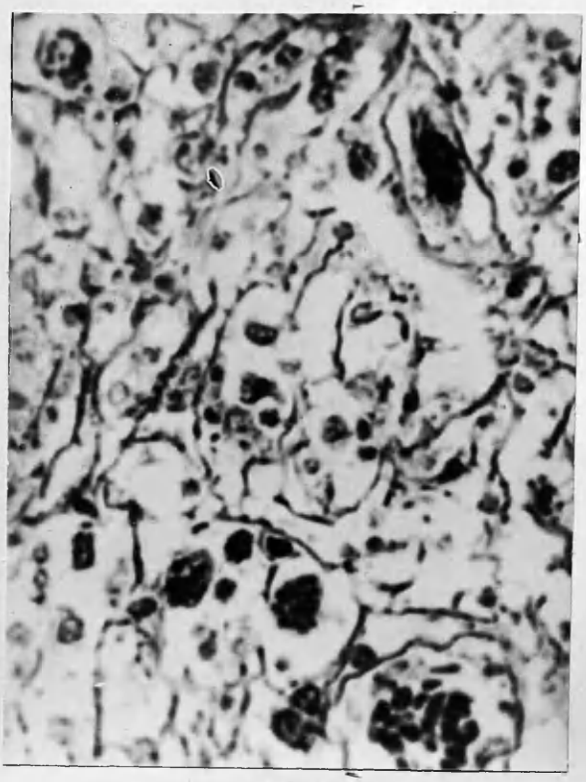


Fig.75.108/39.Chronic Reticulosis.
Gland with fairly copious
interlacing reticulin fibrils.
Silver impregnation.× 500.

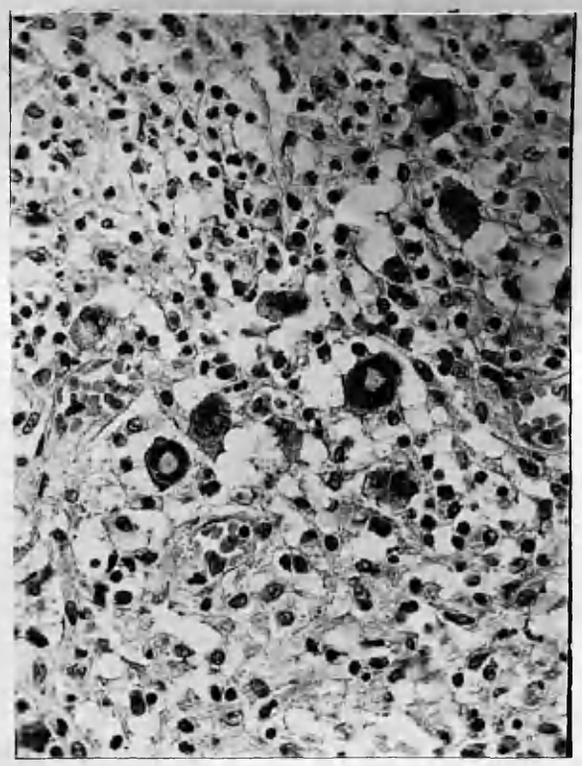


Fig.76.446/37.Chronic Reticulosis.
Cellular area of gland showing many giant cells with unusual nuclei.
H.& E. × 400.

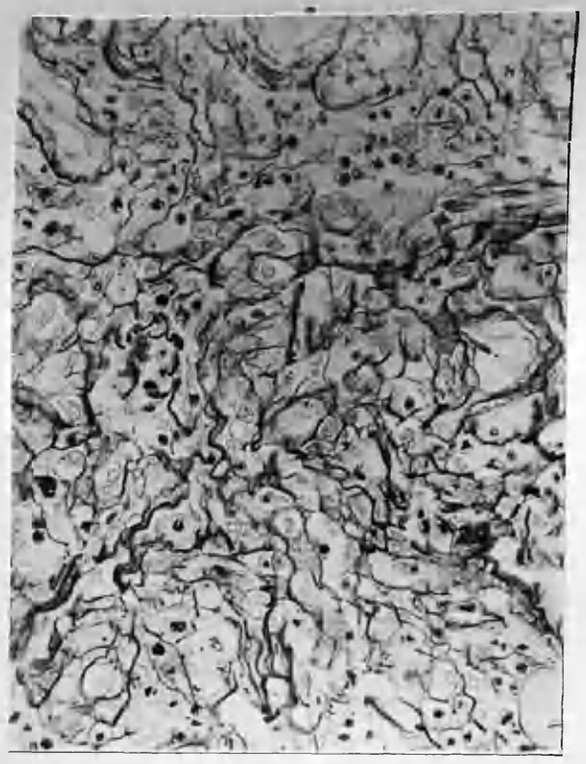


Fig.77.446/37.Chronic Reticulosis.
Gland showing fairly copious reticulin.
Silver impregnation. × 400.

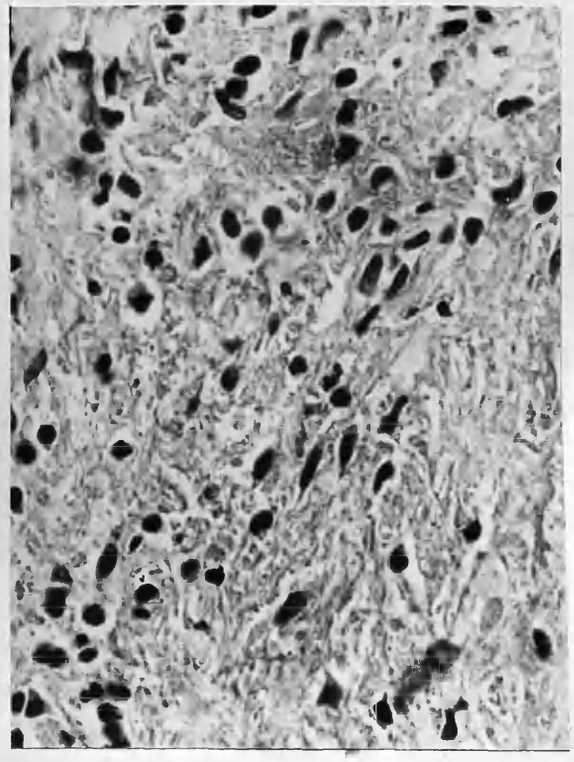


Fig.78.446/37.Chronic Reticulosis.
Gland showing area which is less cellular and more fibrous.
H.& E. × 400.

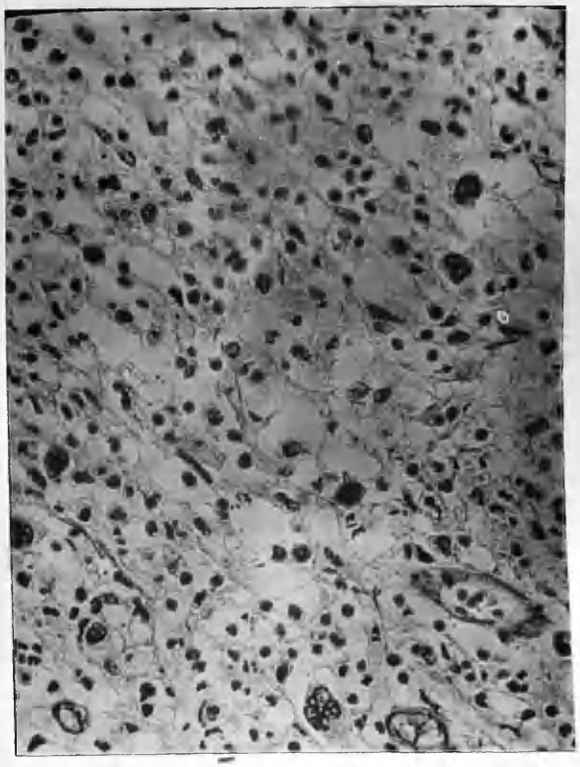


Fig.79.446/37.Chronic Reticulosis.
Gland. Fibrous area showing fine, scanty reticulin.
Silver impregnation. × 400.

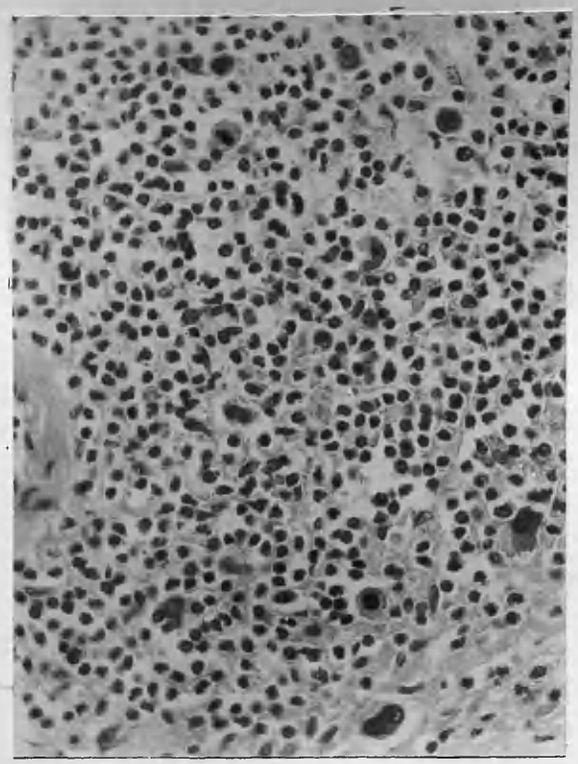


Fig.80.446/37.Chronic Reticulosis Spleen. Malpighian body with hyperplastic reticulum cells and mononuclear giant cells.
H.& E. × 400.

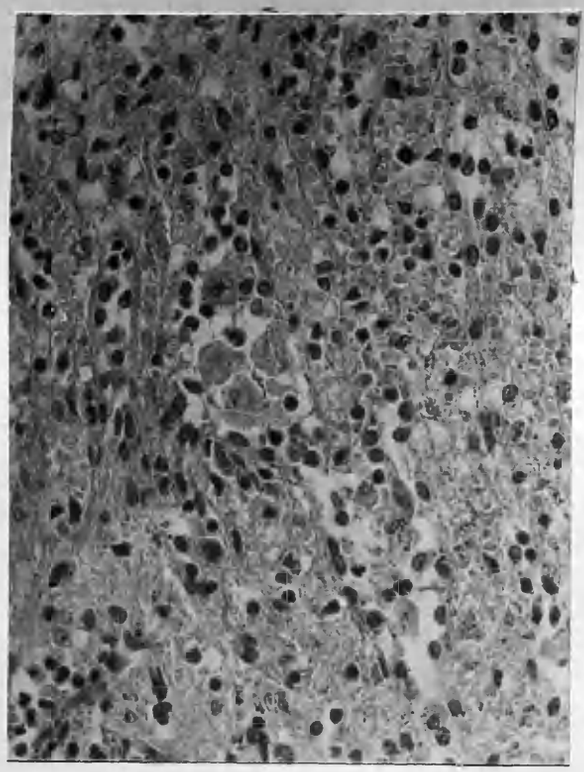


Fig.81.446/37.Chronic Reticulosis Splenic Pulp showing considerable fibrosis and slight vascularity.
H.& E. × 400.

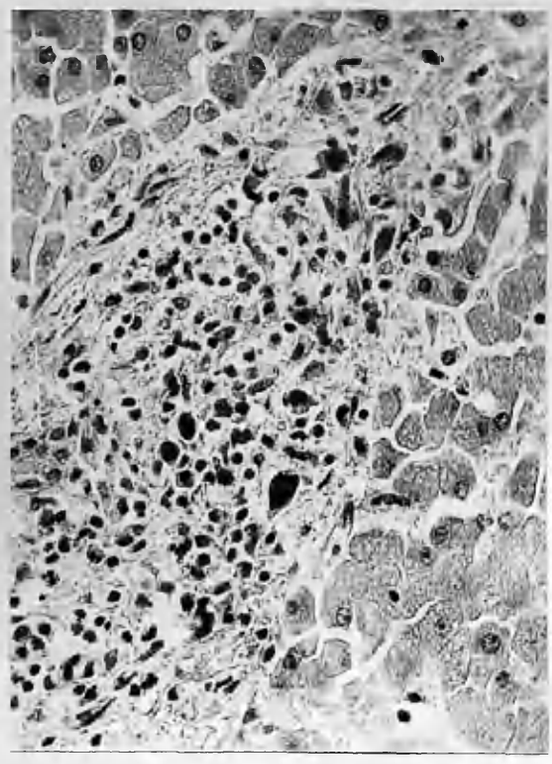


Fig.82.446/37.Chronic Reticulosis. Nodule of typical tissue in liver.
H.& E. × 400.

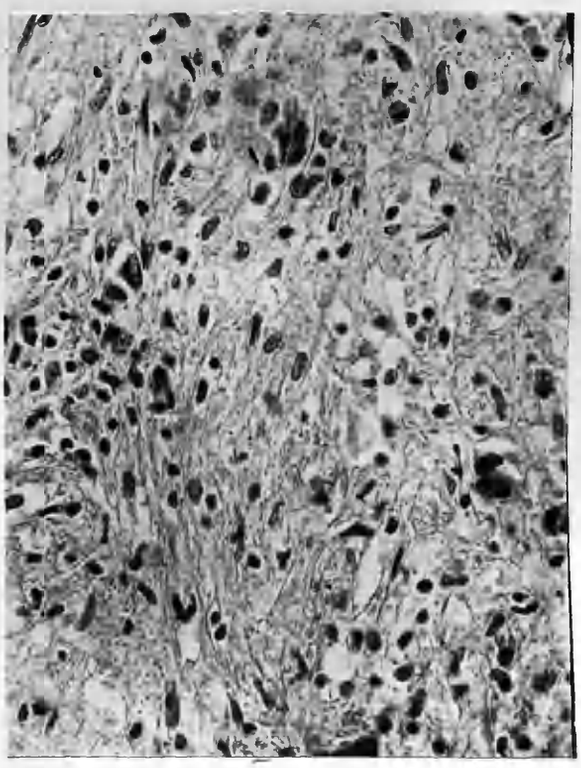


Fig.83.446/37.Chronic Reticulosis. Bone marrow showing typical tissue.
H.& E. × 400.

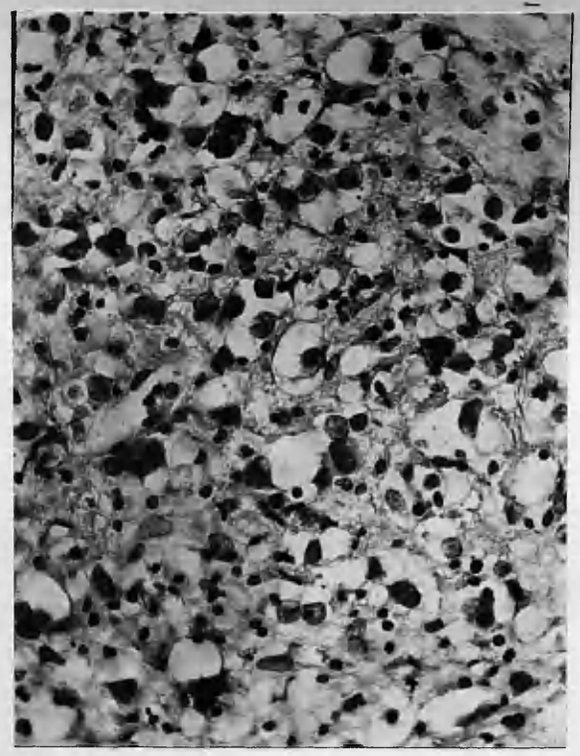


Fig.84.169/38.Chronic Reticulosis.
Gland showing area of
hyperplastic reticulum cells.
H.& E. × 400.

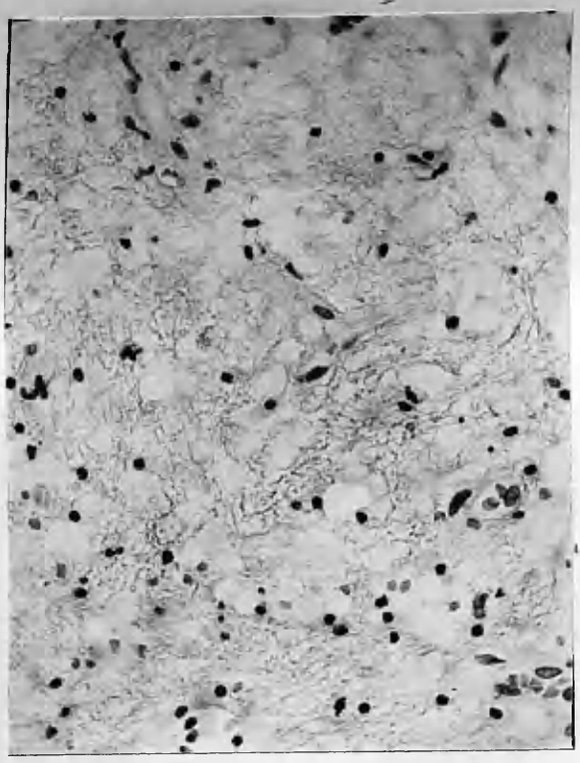


Fig.85.169/38.Chronic Reticulosis.
Gland showing acellular, fibrous
area.
H.& E. × 400.

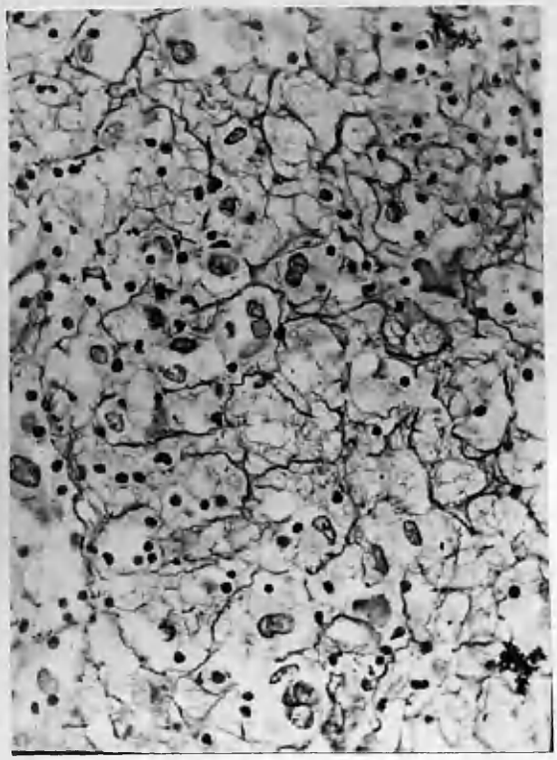


Fig.86.169/38.Chronic Reticulosis.
Gland. Cellular areashowing
fairly copious reticulin.
Silver impregnation. × 400.

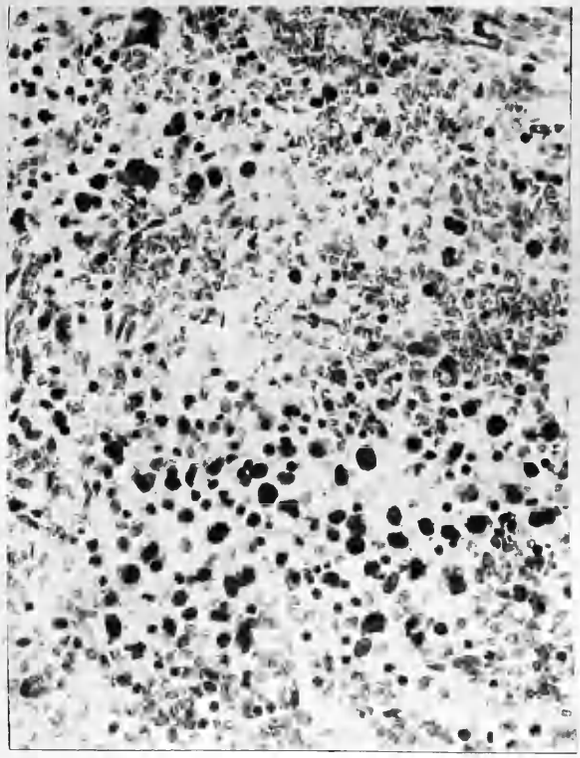
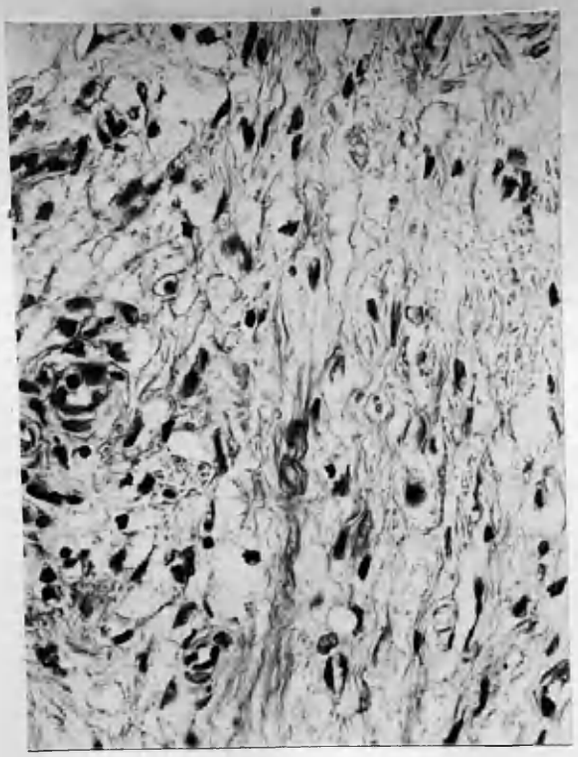


Fig.87.169/38.Chronic Reticulosis.
Splenic pulp showing numerous large
free cells and red corpuscles.
H.& E. × 400.



Fig,88.15950.Chronic Reticulosis.
Gland showing fibrillary tissue.
H.& E.× 250.

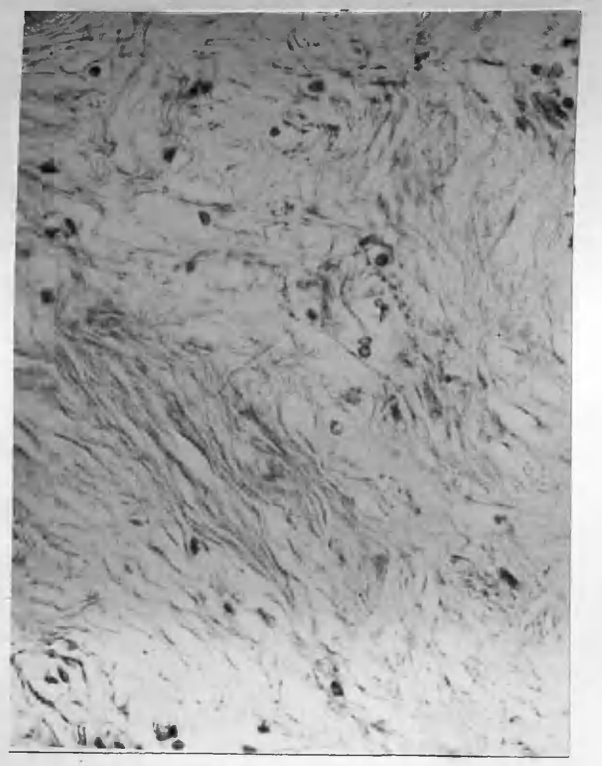


Fig.89.15950,Chronic Reticulosis.
Gland showing fine,scanty reticulin.
Silver impregnation.× 250.

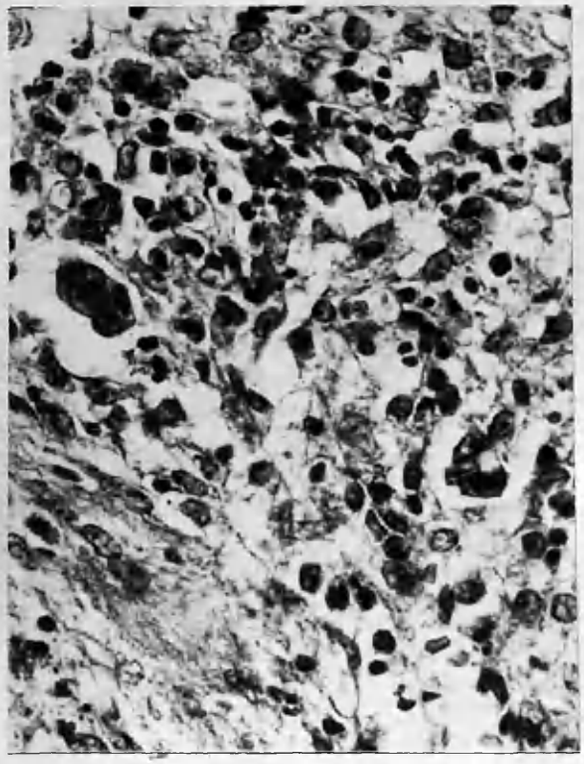


Fig.90.15950.Chronic Reticulosis.
Gland. More cellular area with giant cells.
H.& E.× 400

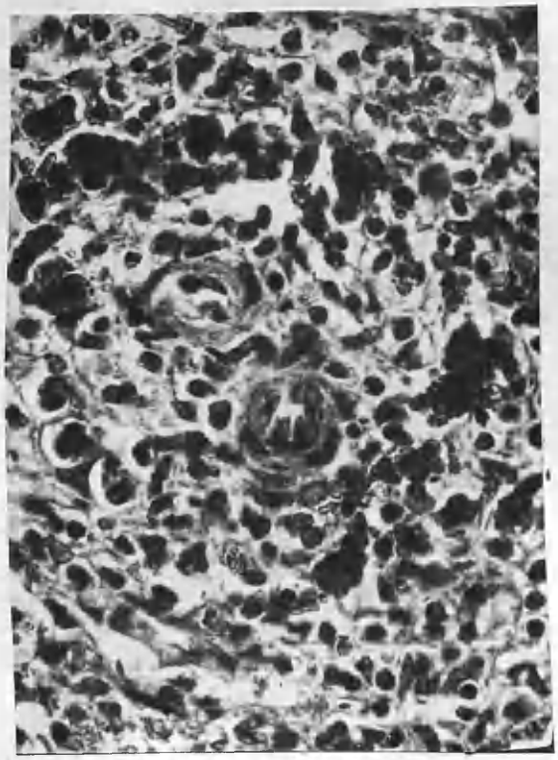


Fig.91.15950.Chronic Reticulosis.
Malpighian body not well defined from pulp. Many large cells and pigment-bearing macrophages.
H.& E.× 500.

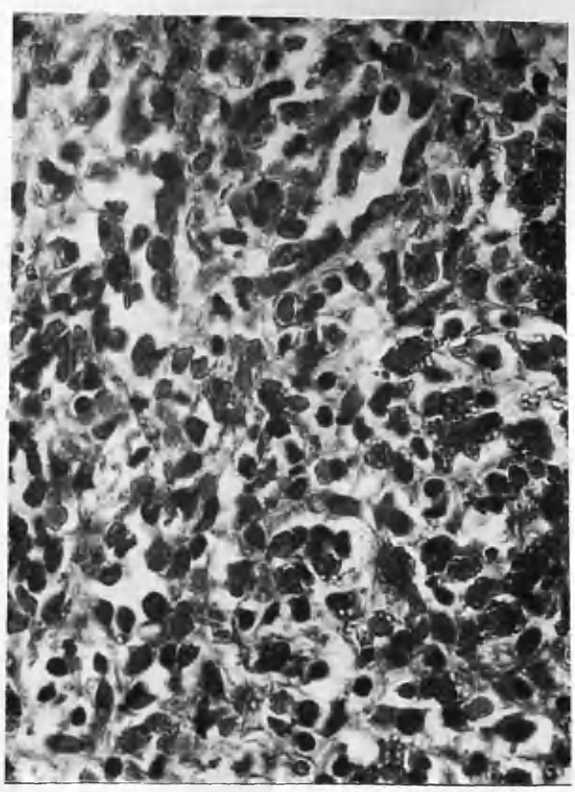


Fig.92.15950.Chronic Reticulosis.
Splenic pulp showing great cellularity and swelling of sinus endothelium. H.& E. × 500.

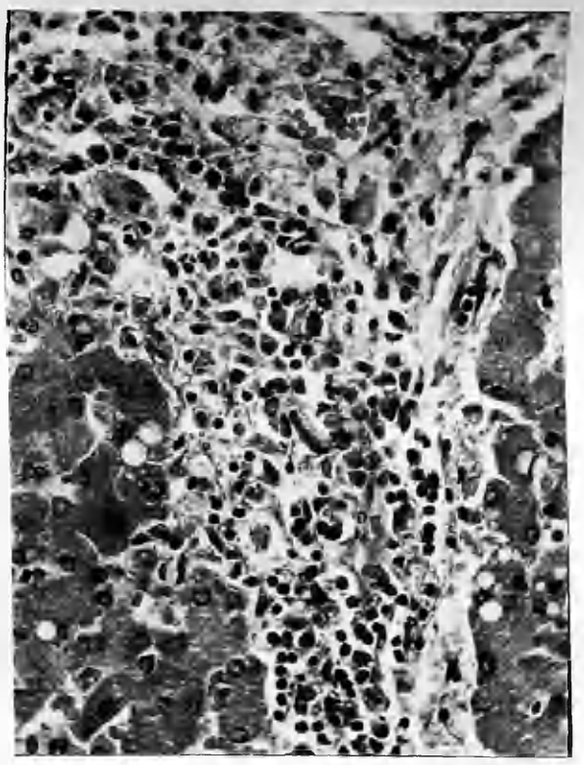


Fig.93.15950.Chronic Reticulosis.
Nodule of cellular tissue from the liver.
H.& E. × 400.

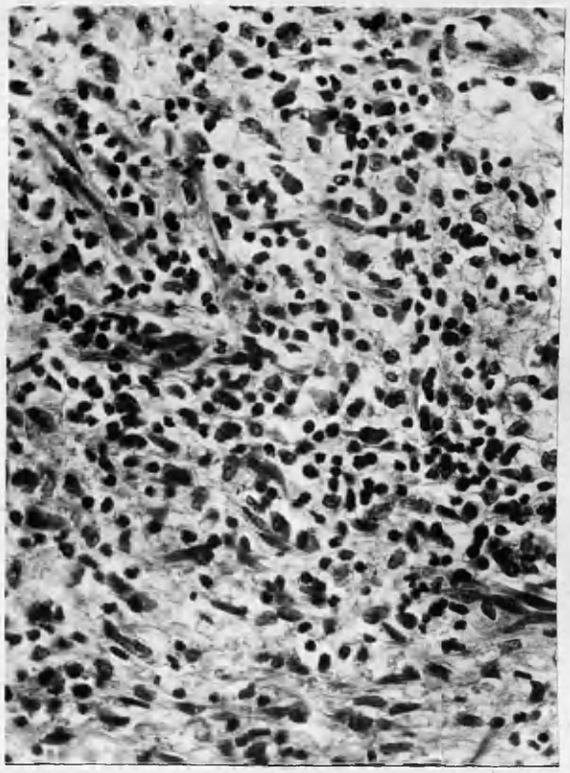




Fig.94.15950.Chronic Reticulosis.
Nodule of cellular tissue from wall of large bronchus.
H.& E. × 400.

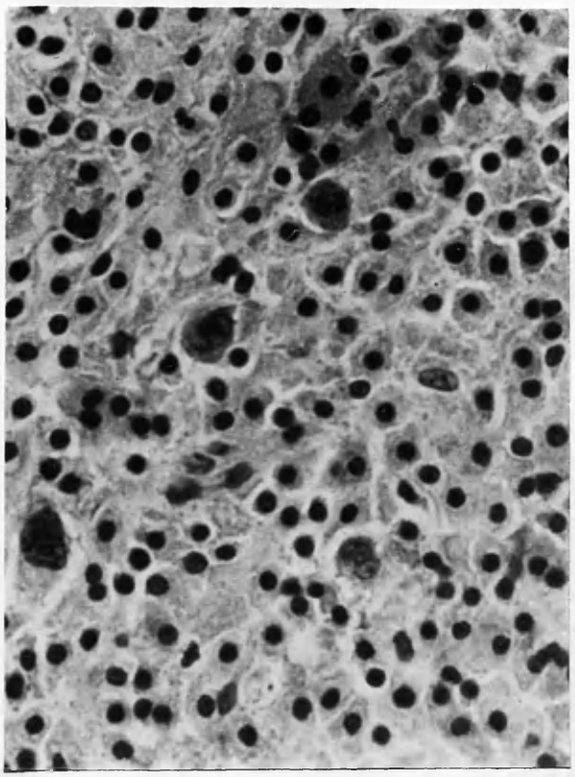


Fig.95.944.Chronic Reticulosis.
Gland showing hyperplastic reticulum cells and giant cells.
H.& E. × 500.

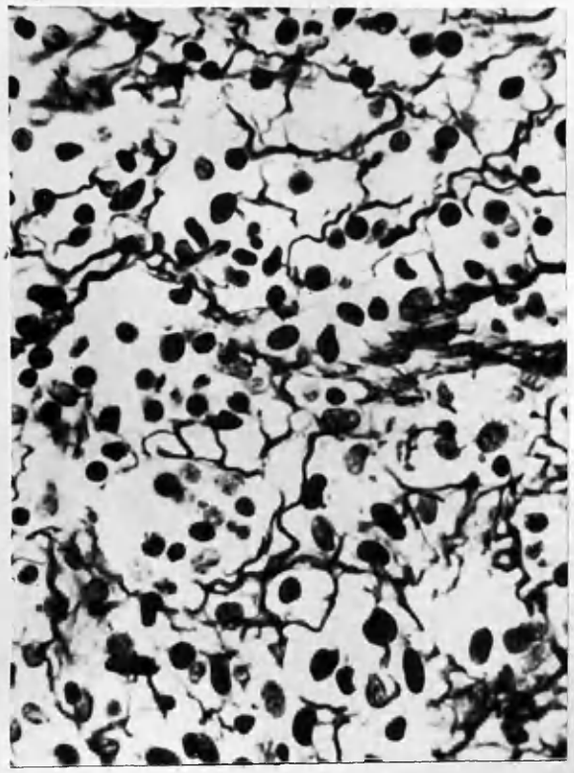


Fig.96.944.Chronic Reticulosis,
Gland showing fairly copious reticulin.
Silver impregnation. × 500.

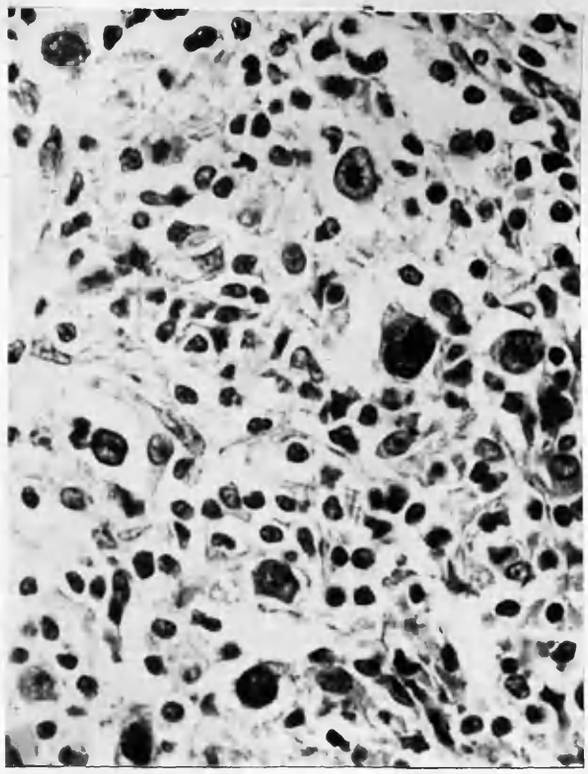


Fig.97.1242.Chronic Reticulosis. Gland showing hyperplasia of reticulum cells, swelling of sinus endothelium & mononuclear giant cells. H.& E. × 500.

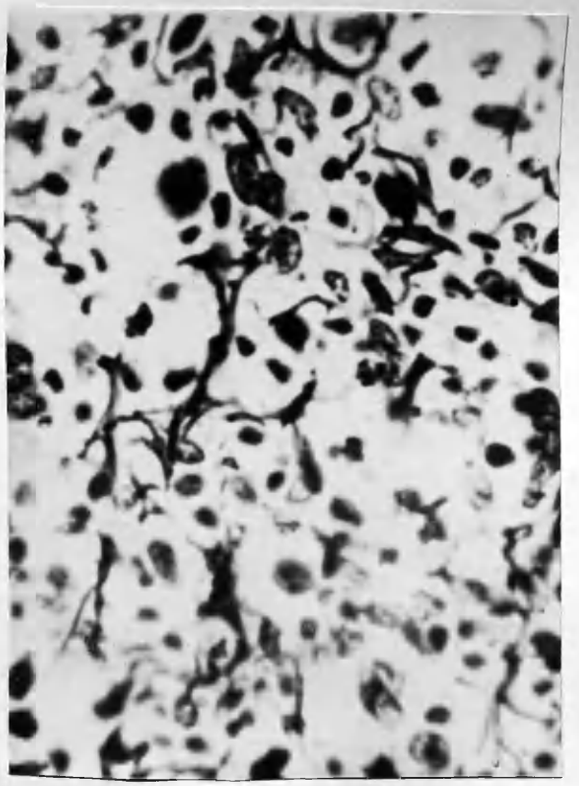


Fig.98.1242.Chronic Reticulosis. Gland to show reticulin. Silver impregnation. × 500.

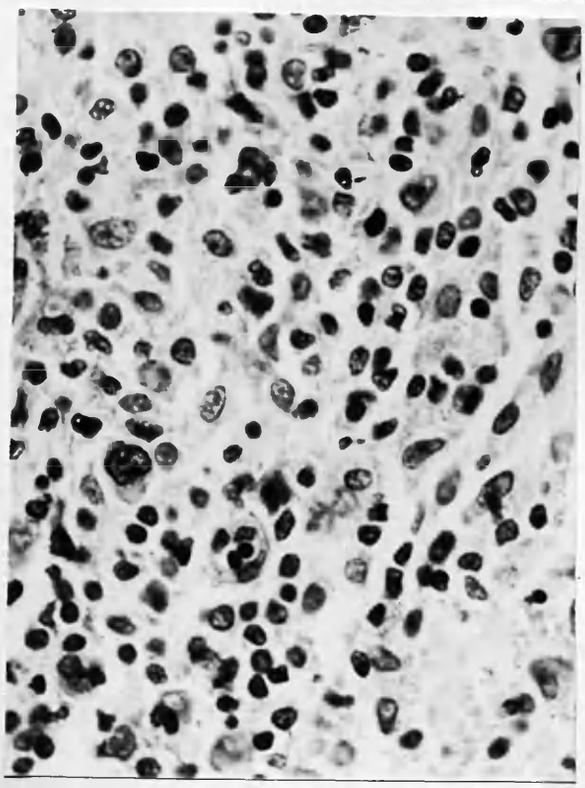


Fig.99.34/37.Chronic Reticulosis. Gland. Hyperplasia of reticulum cells, swelling of sinus endothelium. Also large free cells. H.& E. × 500.

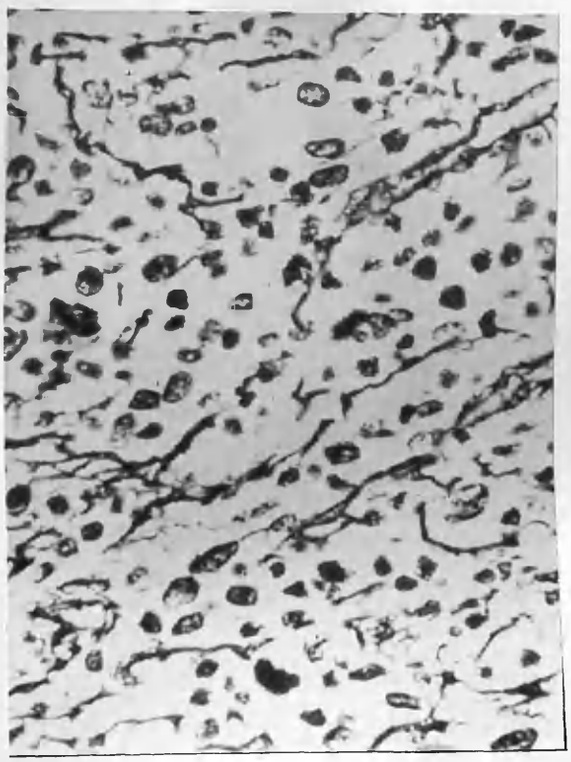


Fig.100.34/37.Chronic Reticulosis. Gland to show reticulin. Silver impregnation. × 500.

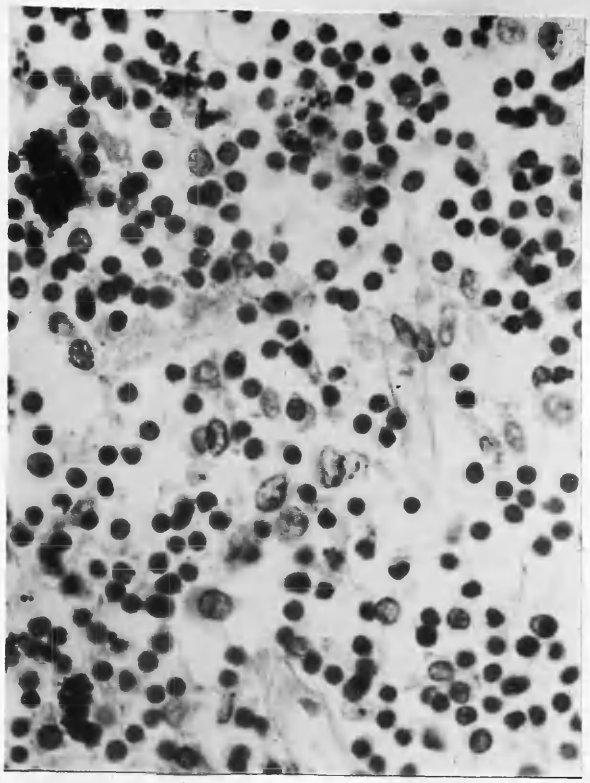


Fig.101.477.Chronic Reticulosis.
Gland showing hyperplasia of reticulum cells,some of which are free.
H.& E.× 500.

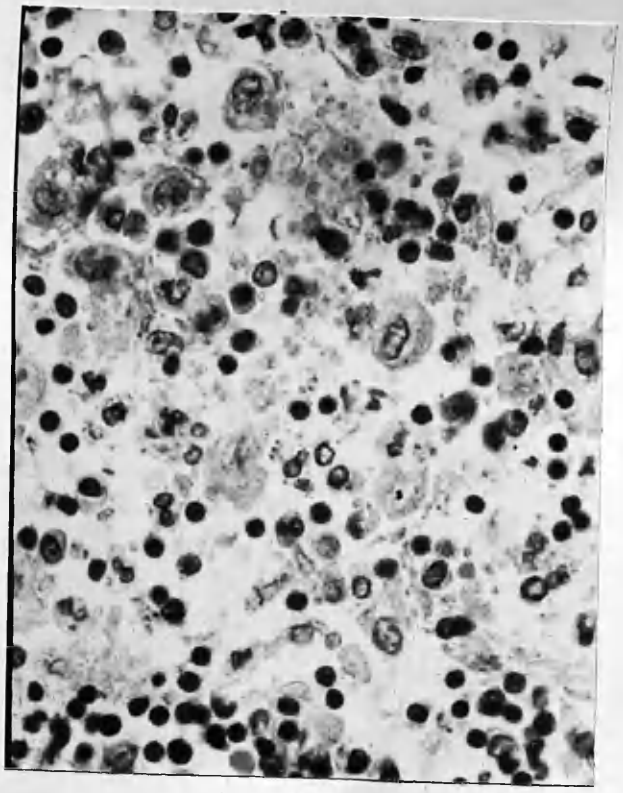


Fig.102.477.Chronic Reticulosis.
Gland showing large phagocytes. with pale nucleus,nuclear rim & nucleolus.
H.& E.× 500.

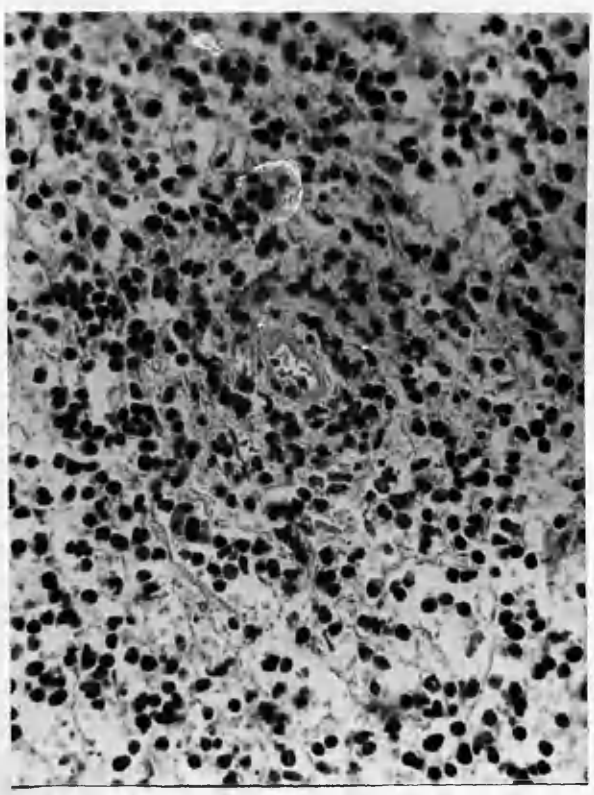


Fig.103.477.Chronic Reticulosis.
Spleen showing lack of definition of Malpighian bodies.
Pulp very cellular.
H.& E.× 200.

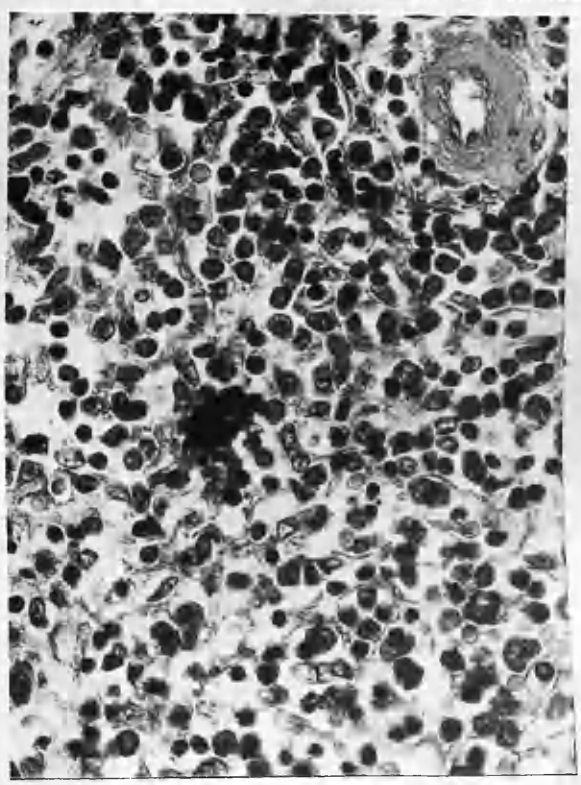
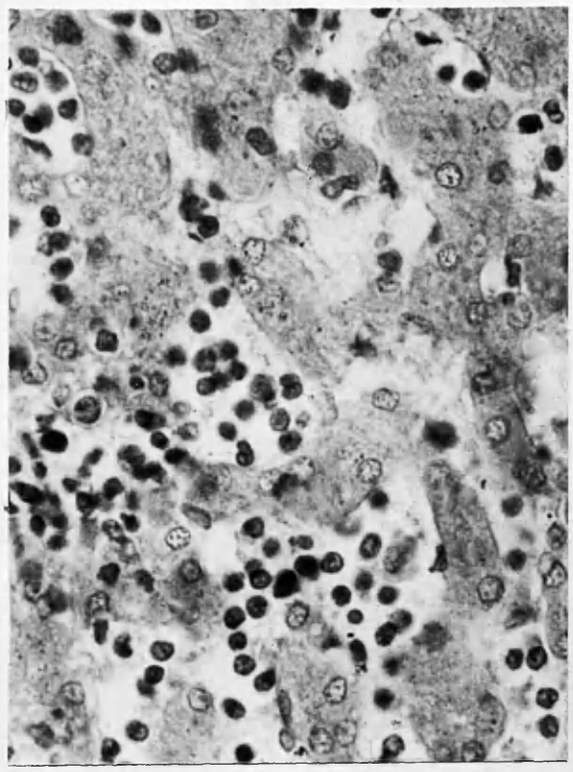


Fig.104.477.Chronic Reticulosis.
Malpighian body showing hyperplastic reticulum cells and a phagocyte loaded with pigment.
H.& E.× 500.



105

Fig.105.477.Chronic Reticulosis.
Liver showing rather diffuse
round celled infiltration.
H.& E.× 500.

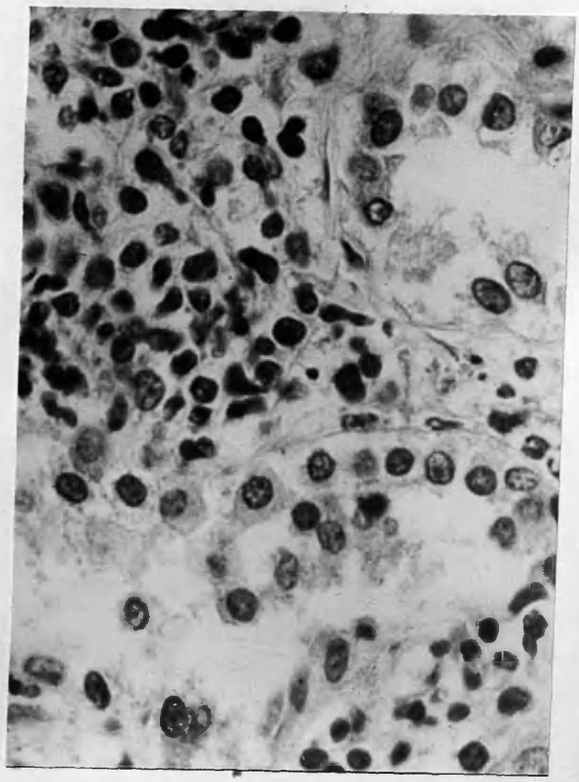


Fig.106.477.Chronic Reticulosis.
Kidney showing area of cellular
infiltration.
H.& E.× 500.

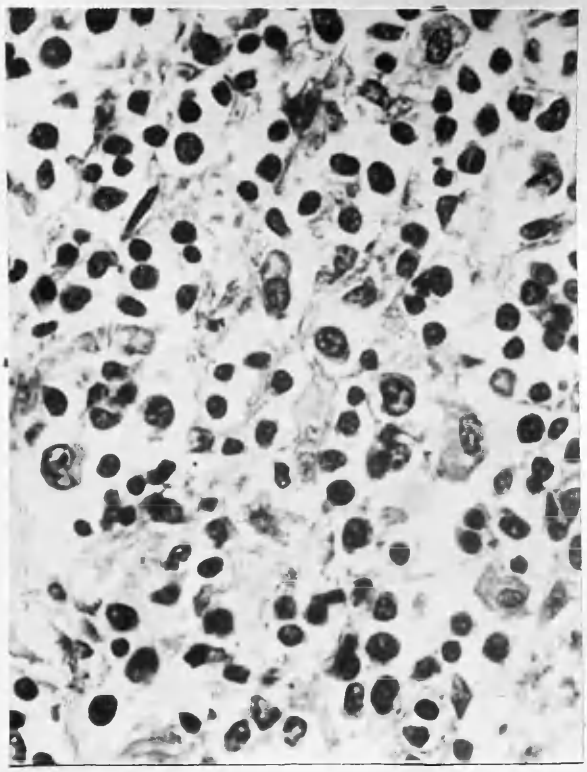


Fig.107.16002.Chronic Reticulosis. Gland with hyperplasia of reticulu cells. Free cells like monocytes. H.& E.× 500.

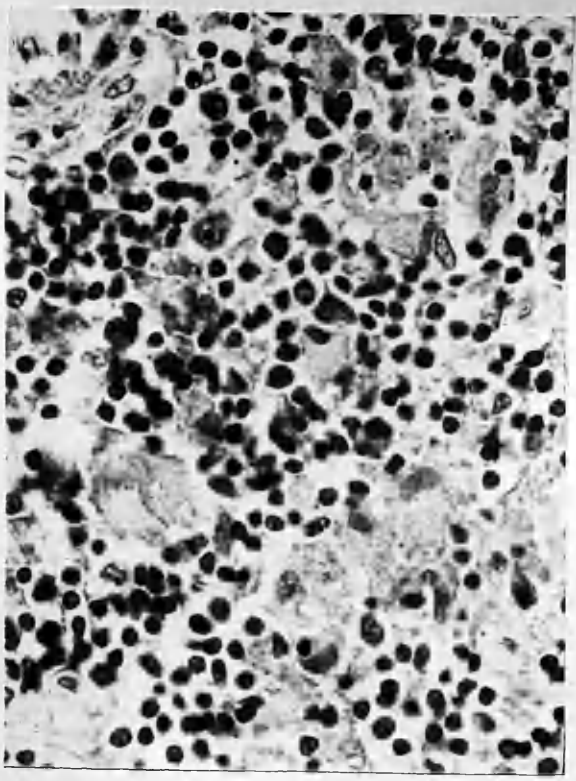


Fig.108.16002.Chronic Reticulosis. Spleen.Malpighian body with large free monocytoid cells and phagocytic plaques. H.& E.× 500.

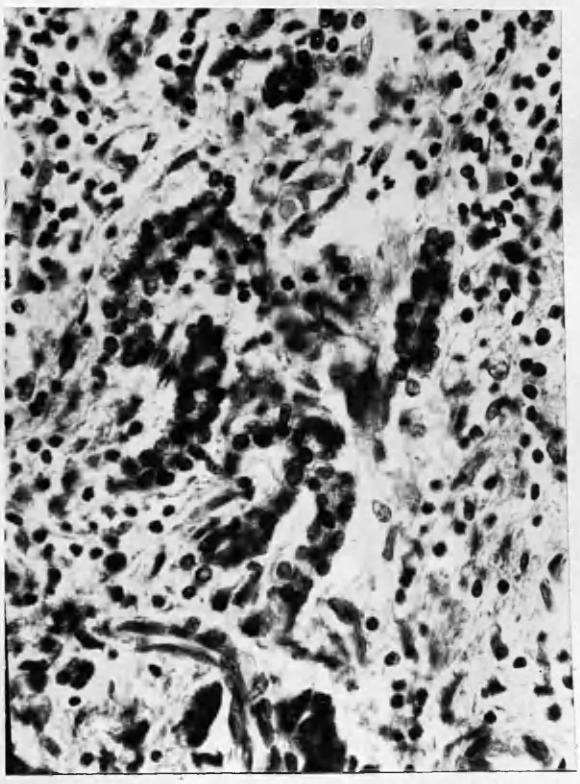


Fig.109.16002.Chronic Reticulosis. Liver showing surviving bile ducts in area of infiltration. H.& E.× 300.

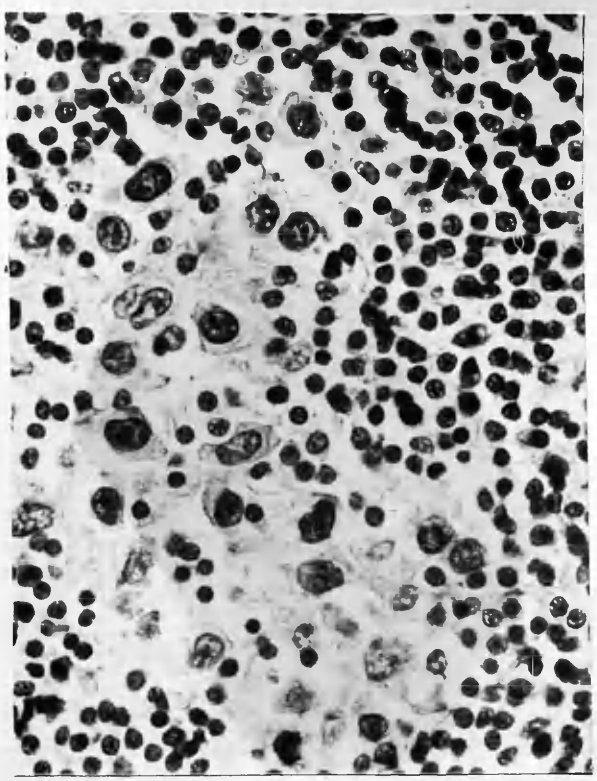


Fig.110.308/34.Chronic Reticulosis
Gland showing hyperplastic reticulum cells,some free. Many lymphocytes remain.
H.& E.× 500·

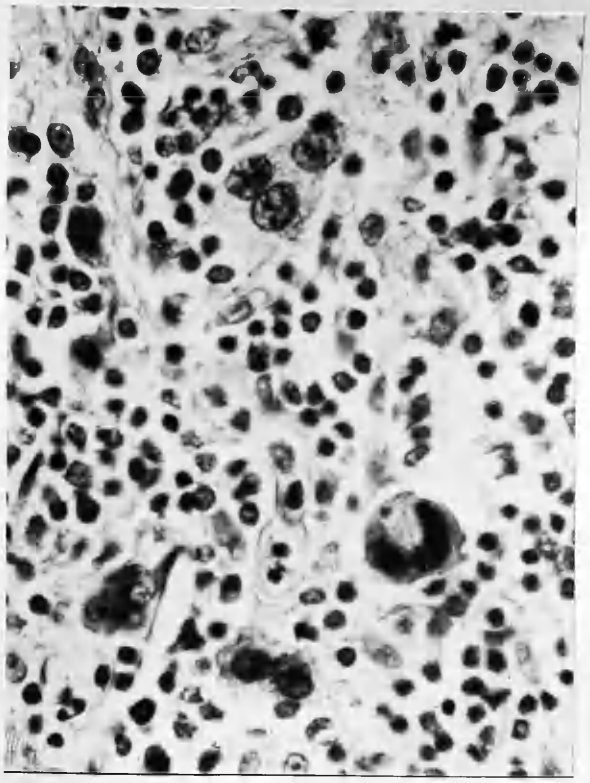


Fig.111.308/34.Chronic Reticulosis
Another area of same gland with hyperplasia of reticulum cells and giant cell formation.
H.& E. × 500.

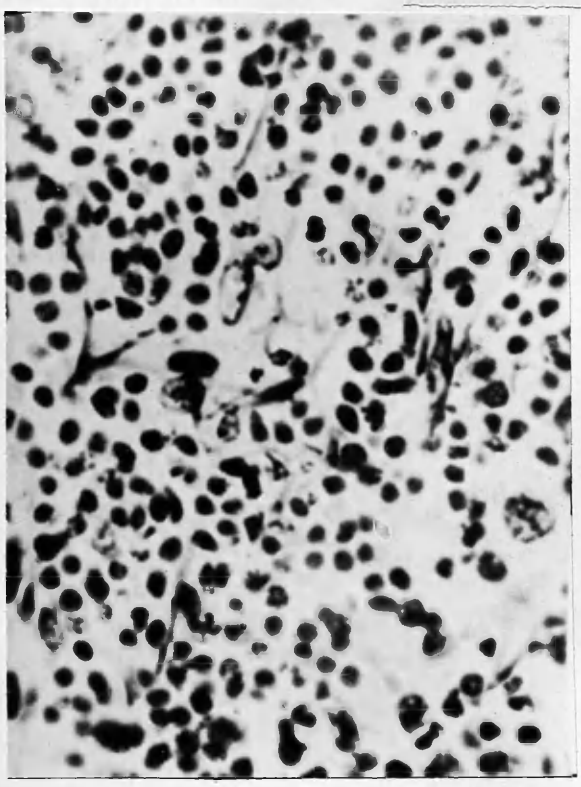


Fig.112.308/34.Chronic Reticulosis
Gland showing scanty reticulin.
Silver impregnation.× 500.

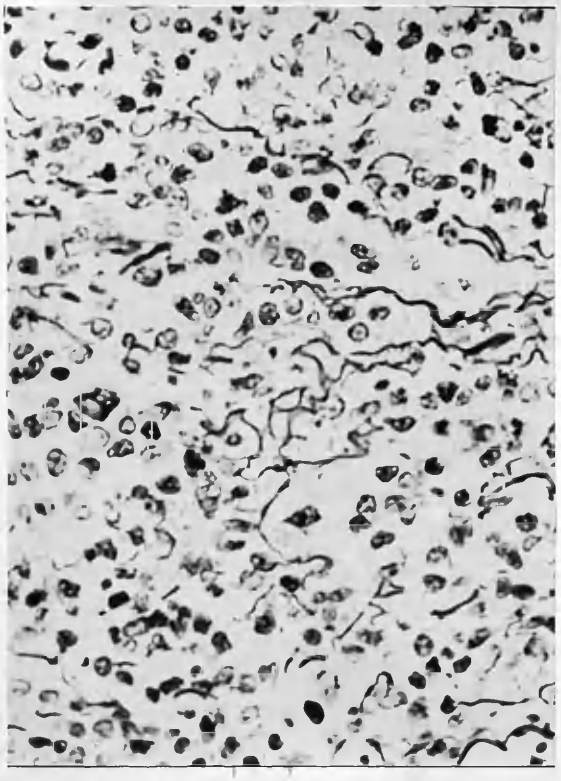


Fig.113.1319.Chronic Reticulosis.
Showing fine scanty reticulin.
Silver impregnation. × 400.

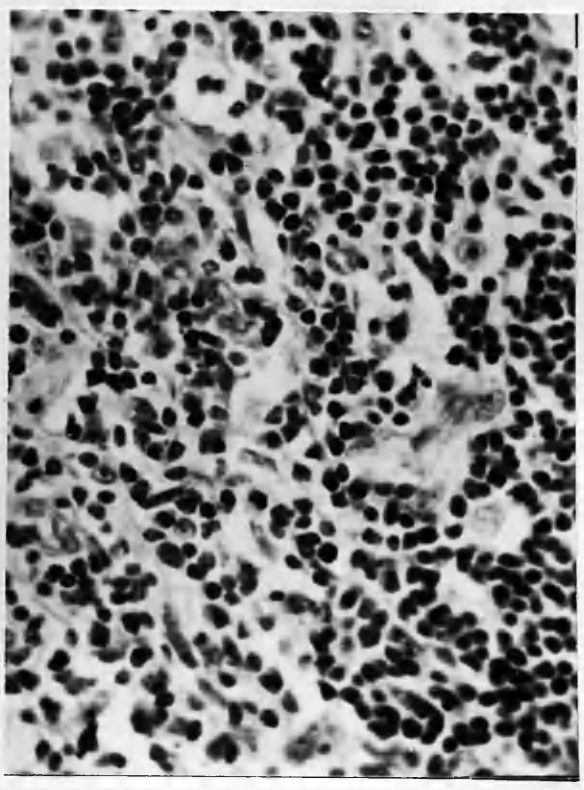


Fig.114.2005.Chronic Reticulosis.
Gland showing very early
hyperplasia of reticulum cells
with numerous surviving
lymphocytes. H.& E. × 500.

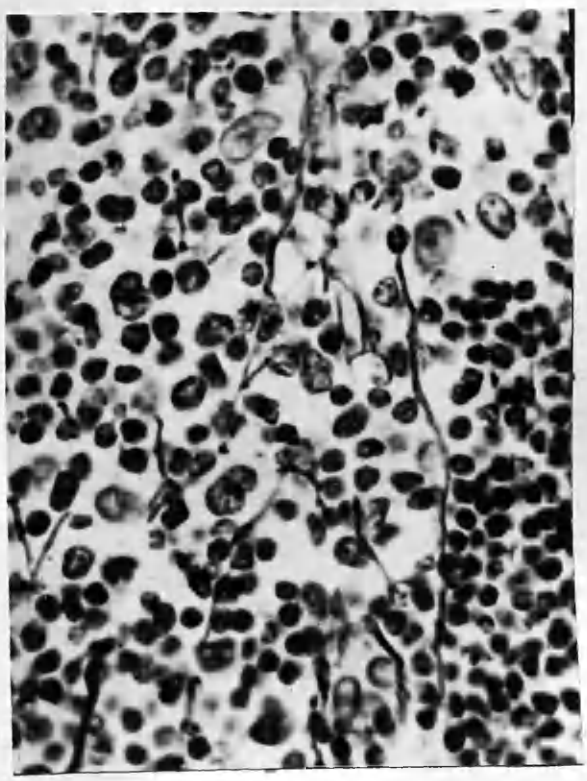


Fig.115.2005.Chronic Reticulosis.
Gland showing hyperplastic
reticulum cells and some
reticulin.
Silver impregnation. × 500

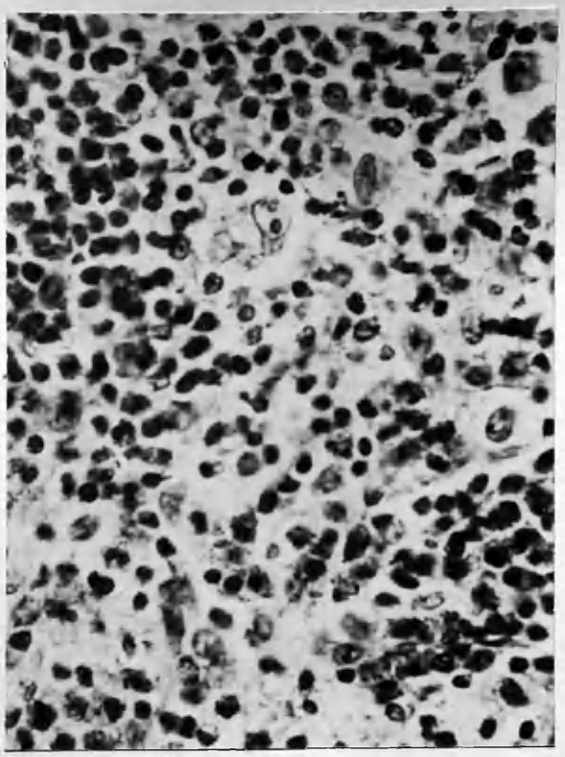


Fig.116.6/10.Chronic Reticulosis.
Gland showing hyperplasia of reticulum cells.
H.& E. × 500.

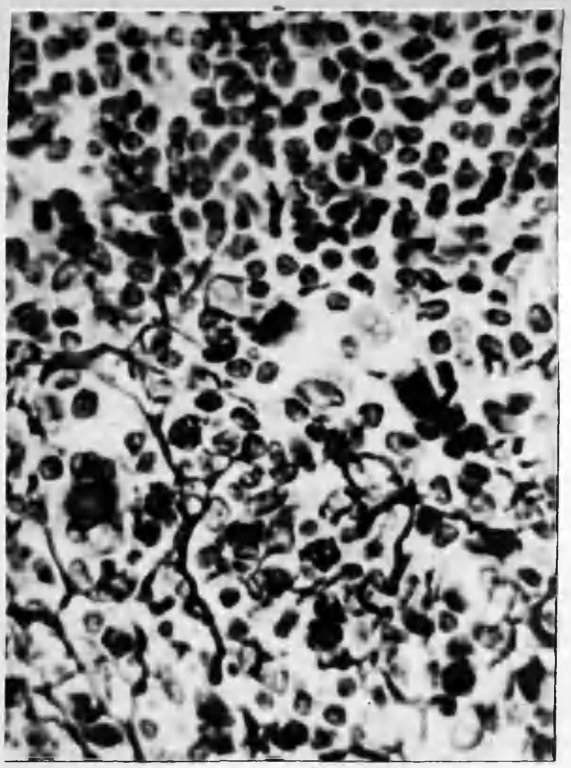


Fig.117.6/10.Chronic Reticulosis.
Gland to show reticulin.
Silver impregnation. × 500.

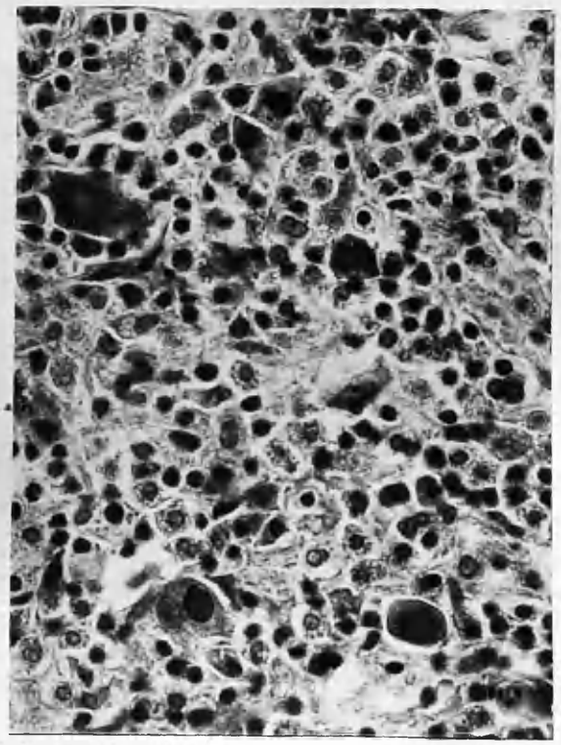


Fig.118.196.Chronic Reticulosis.
Gland showing hyperplastic reticulum cells and giant cells.
H.& E. × 500.

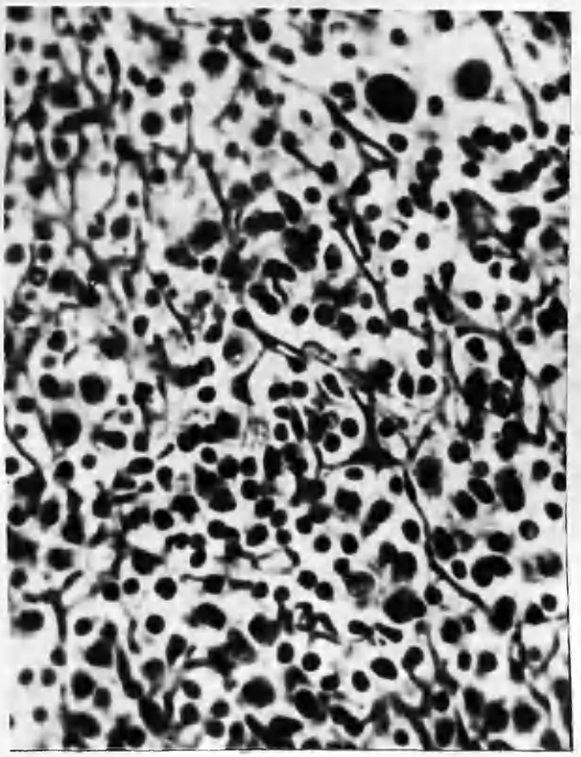


Fig.119.196.Chronic Reticulosis.
Gland to show fairly copious reticulin.
Silver impregnation. × 500.

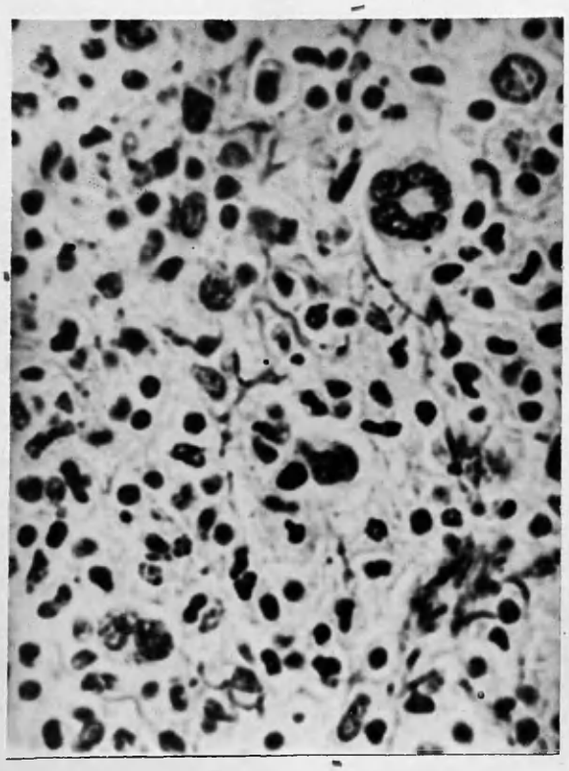


Fig.120.1713.Chronic Reticulosis.
Gland showing hyperplasia of reticulum cells and giant cell formation.
H.& E. × 500.

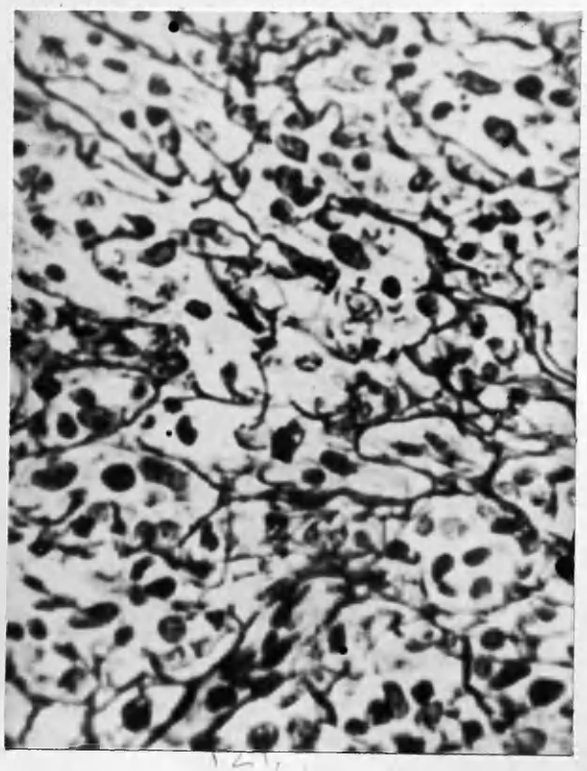


Fig.121.1713.Chronic Reticulosis.
Gland to show fairly copious reticulin.
Silver impregnation. × 500.

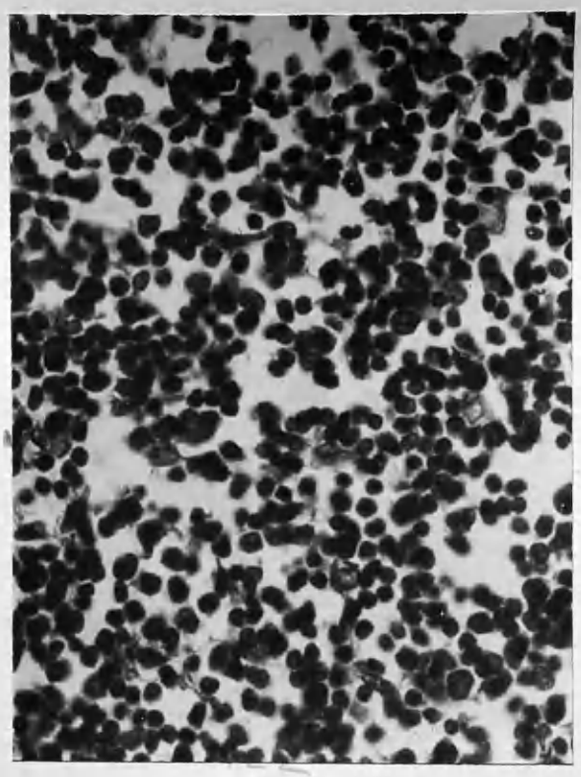


Fig.122.176/37.Lymphatic Leukaemia. Gland showing falrly uniform cellularity. Very little hyperplasia of reticulum cells. H.& E.× 500.

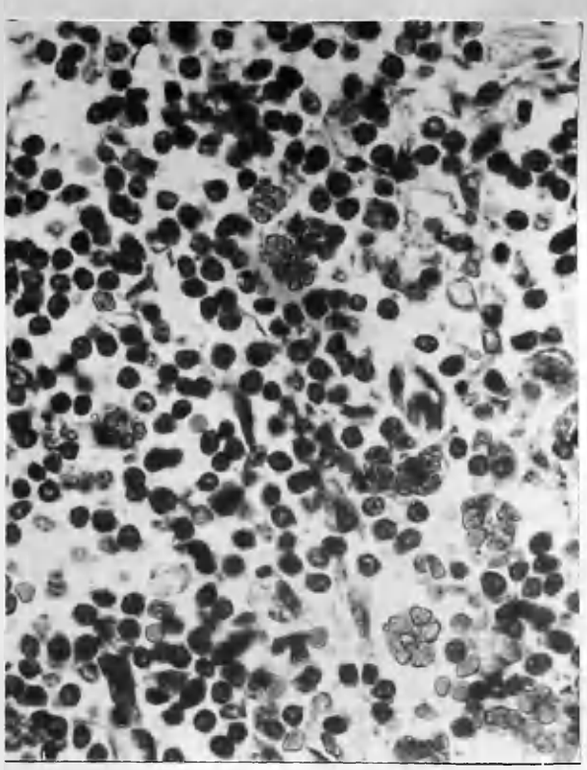


Fig.123.55/37.Lymphatic Leukaemia. Gland showing some hyperplasia of reticulum cells with formation of phagocytes. H.& E. × 500.

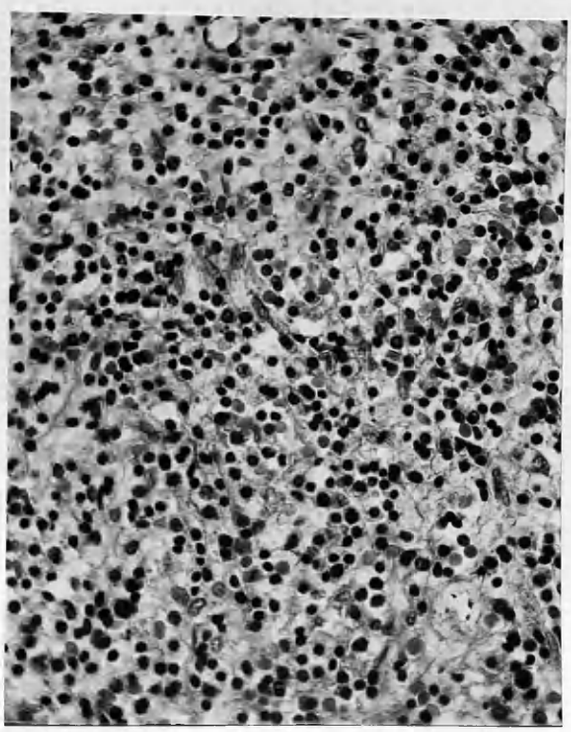


Fig.124.55/37. Lymphatic Leukaemia. Bone marrow to show uniform cellularity. H.& E. × 400.

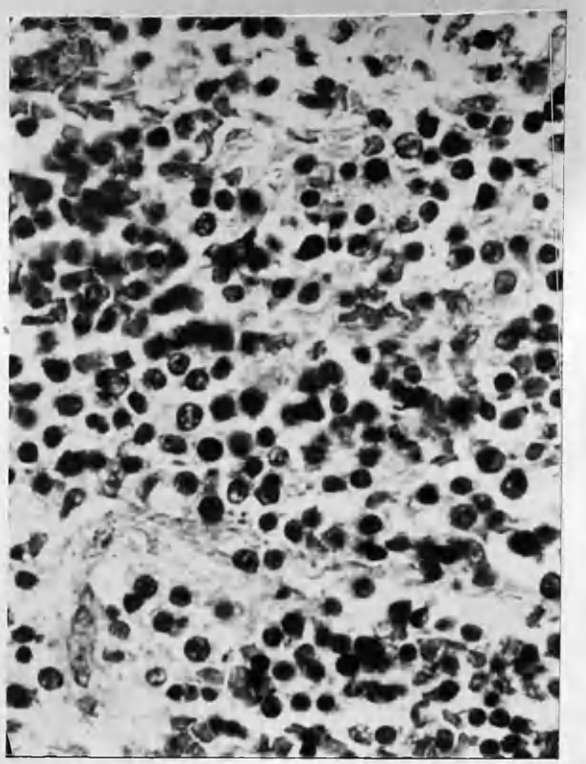


Fig.125.16184.Neoplastic Reticulosis. Tumour from small bowel.
H.& E. × 500

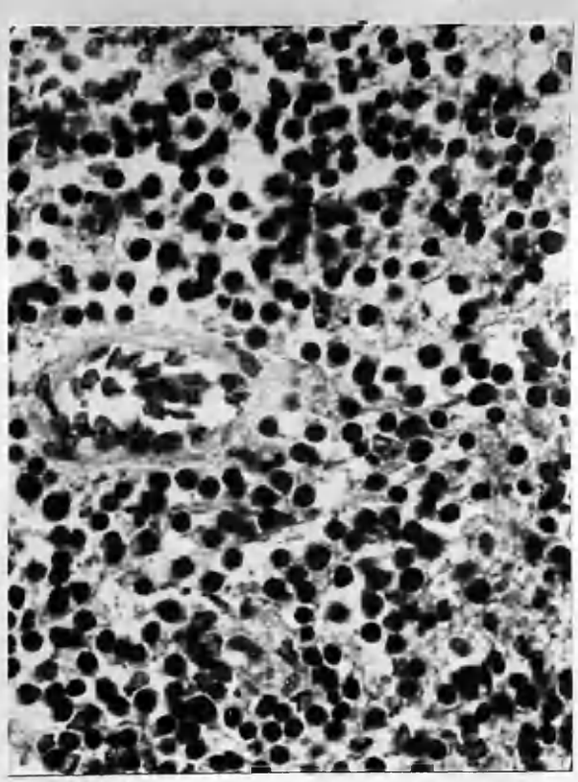
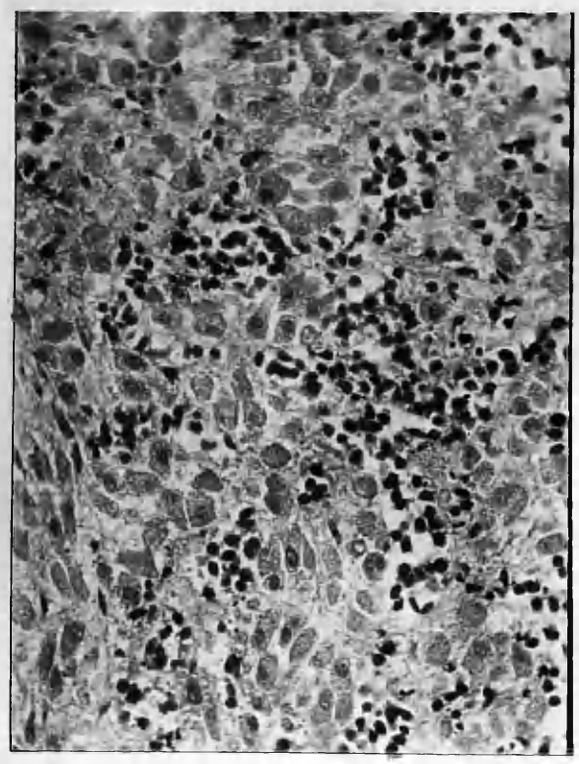


Fig.126.16184. Neoplastic Reticulosis. Spleen to show general cellularity also lack of definition of Malpighian bodies.
H.& E. × 500.



Flg.127.16184. Neoplastic Reticulosis. Suprarenal to show diffuse infiltration.
H.& E. × 400.

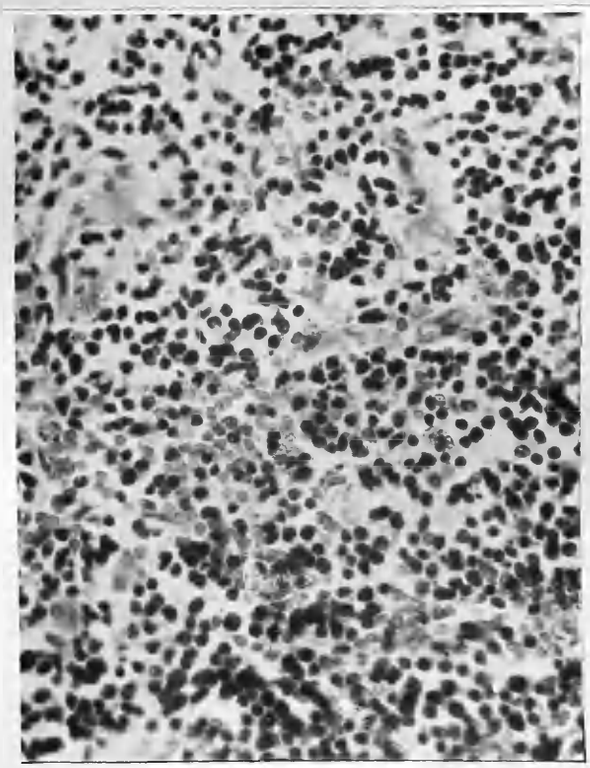


Fig.128.16184. Neoplastic Reticulosis. Tumour Nodule from liver.
H.& E. × 400.

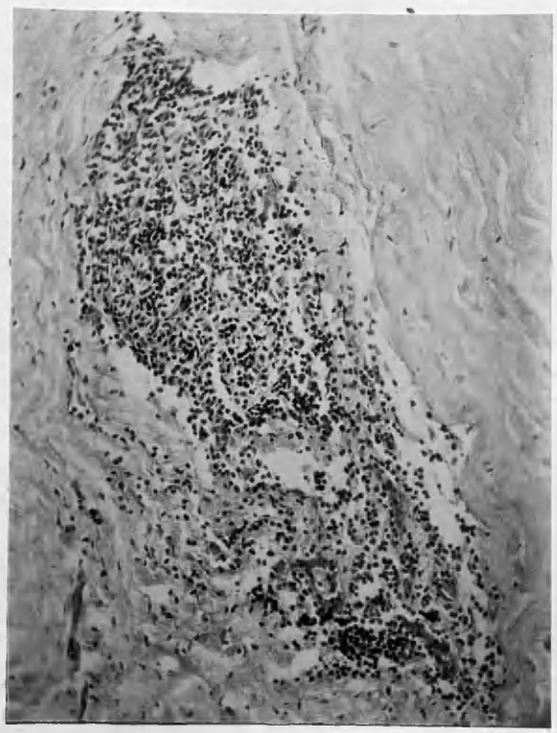


Fig.129.16184. Nepplastic Reticulosis. Tumour nodule from pericardium, around a small vessel.
H.& E. × 200.

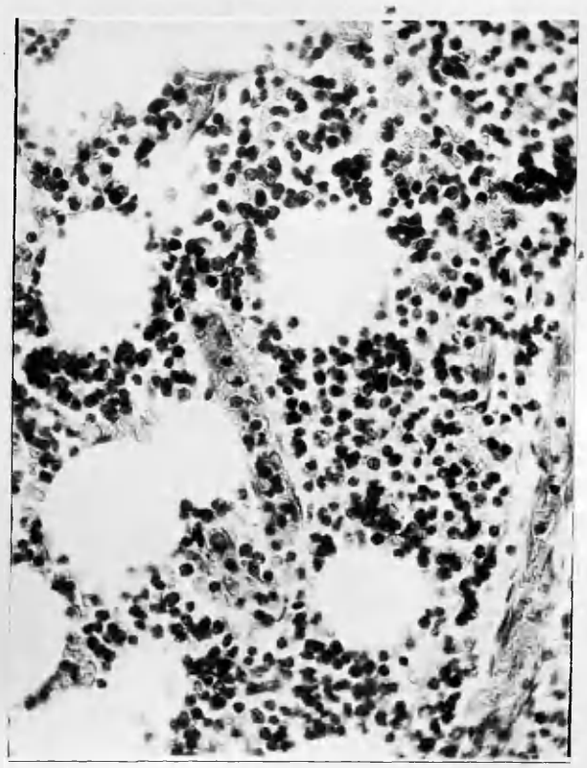


Fig.130.16184. Neoplastic Reticulosis. Tumour nodule from peritoneal surface of bowel.
H.& E. × 400.

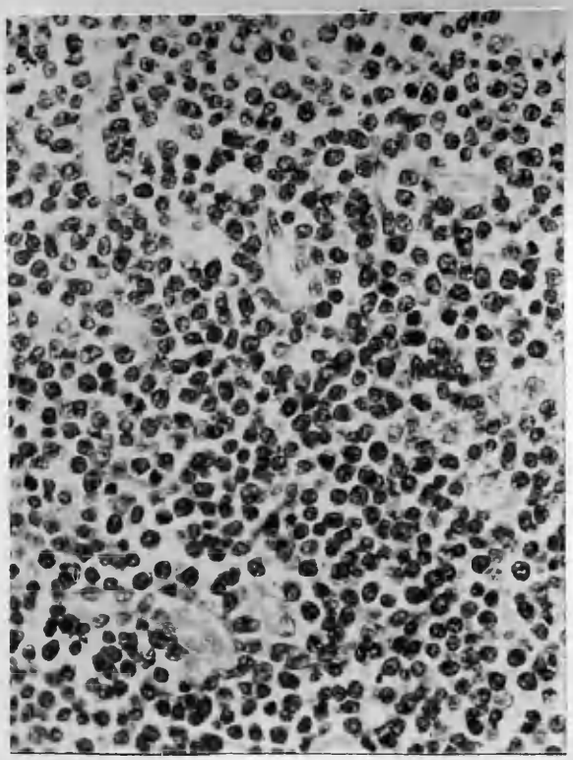


Fig.131.15923.Neoplastic Reticulosis. Tumour showing uniform cellularity. H.& E. × 400.

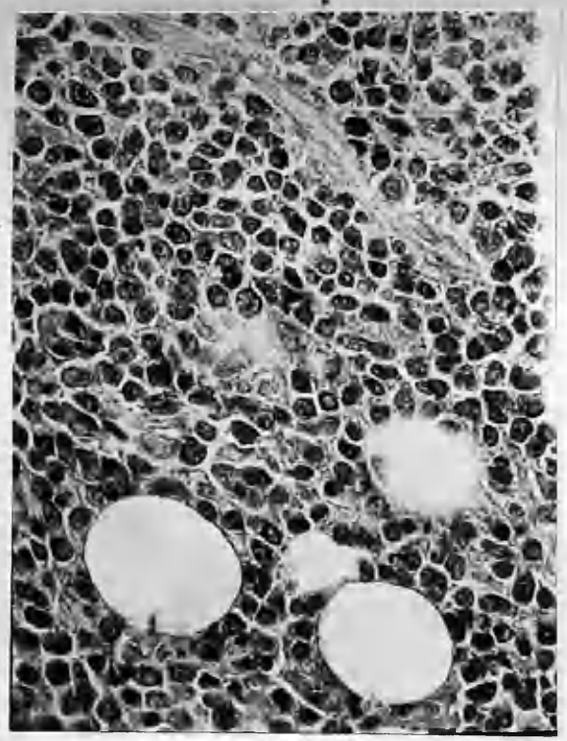


Fig.132.15923. Neoplastic Reticulosis. Tumour showing syncytial arrangement of cells and tendency to endothelial formation. H.& E.× 500.

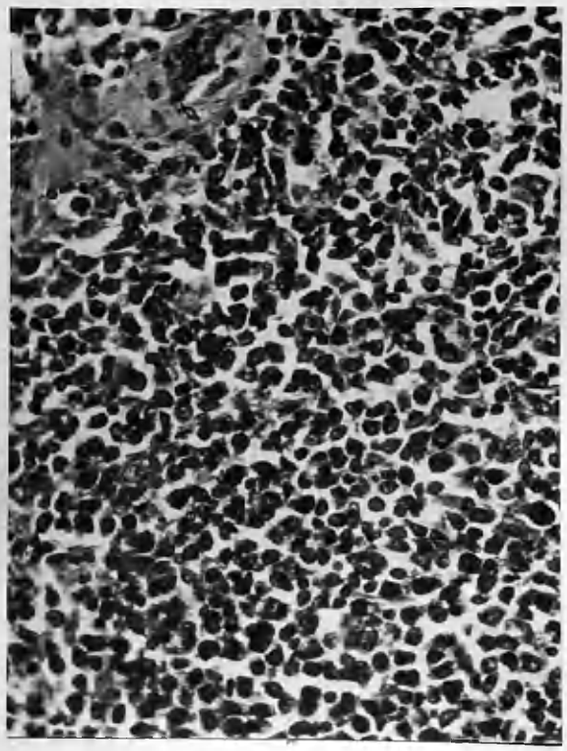


Fig.133.15923. Neoplastic Reticulosis. Spleen to show uniformity of cells and lack of definition of Malpighian bodies. H.& E.× 400.

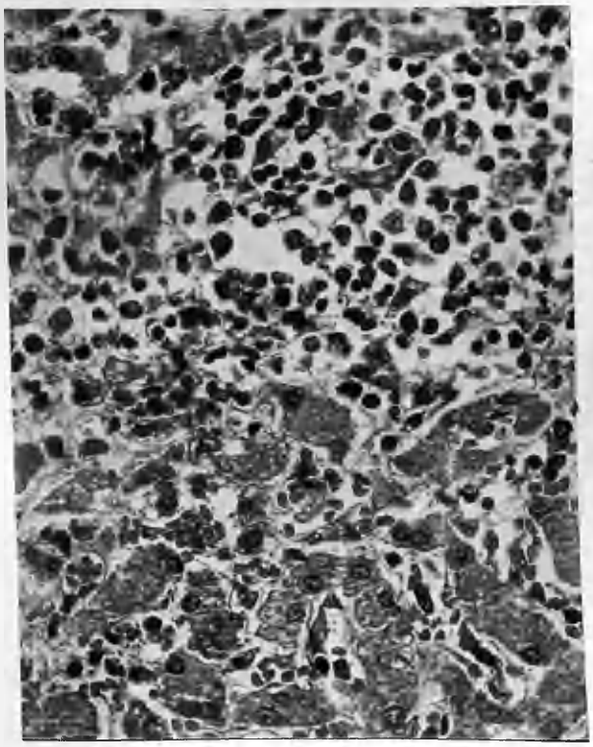


Fig.134.15923. Neoplastic Reticulosis.To show destruction of liver cells and infiltration with tumour cells. H.& E.× 500.

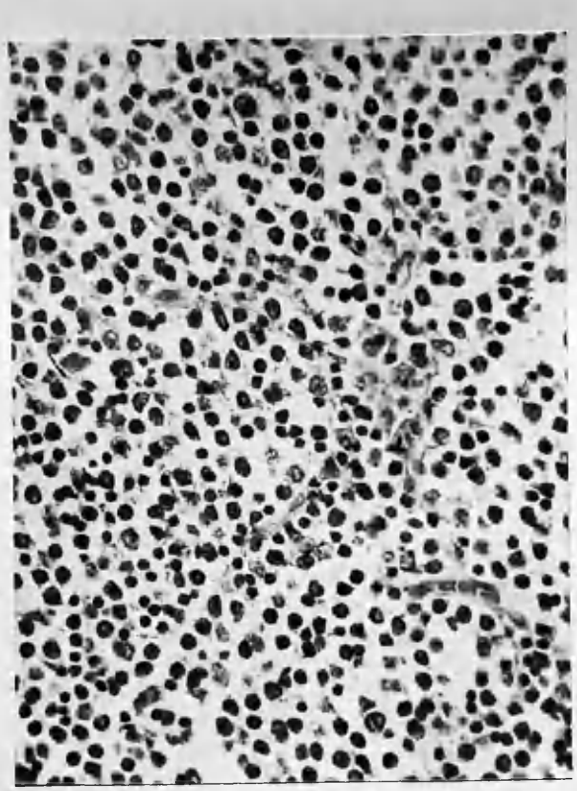


Fig.136.700. Neoplastic Reticulosis. Gland showing uniform cellularity. Reticulum cells scanty.
H.& E.× 400.

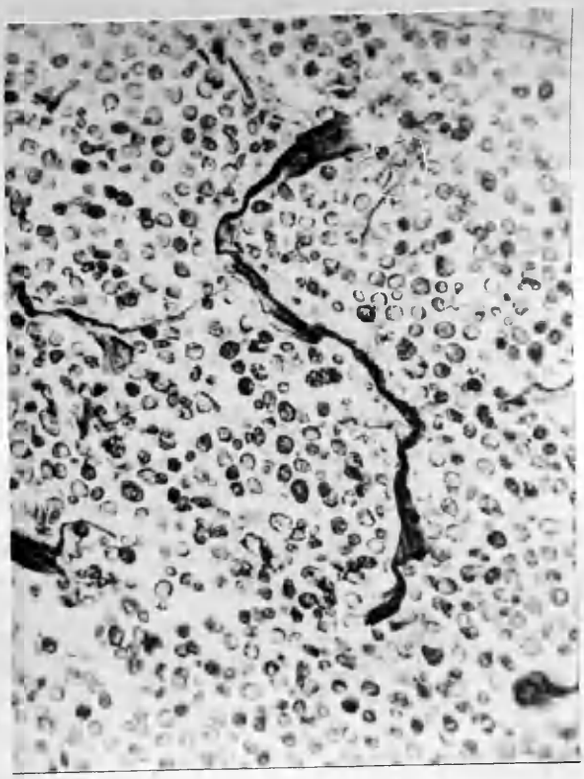


Fig.137. 700. Neoplastic Reticulosis. Gland to show scanty reticulin.
Silver impregnation. × 400

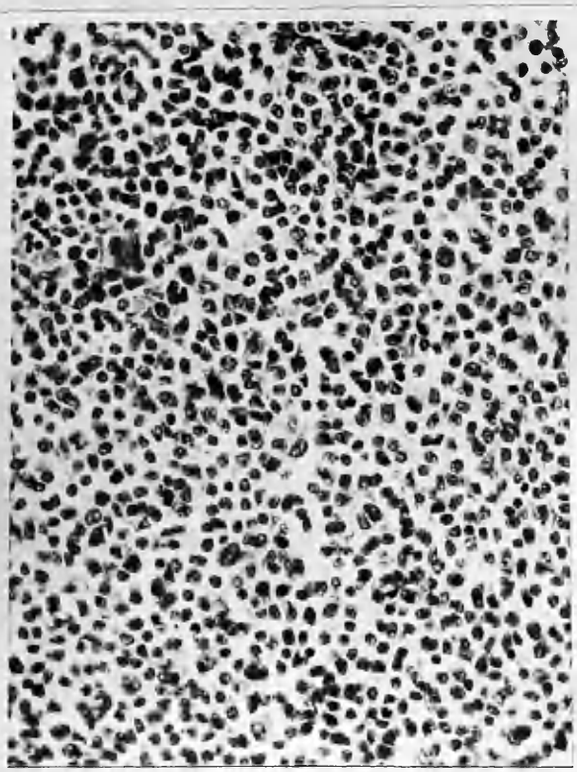


Fig.138. 782. Neoplastic Reticulosis. Gland similar to 700 but cells less uniform.
H.& E. × 400.

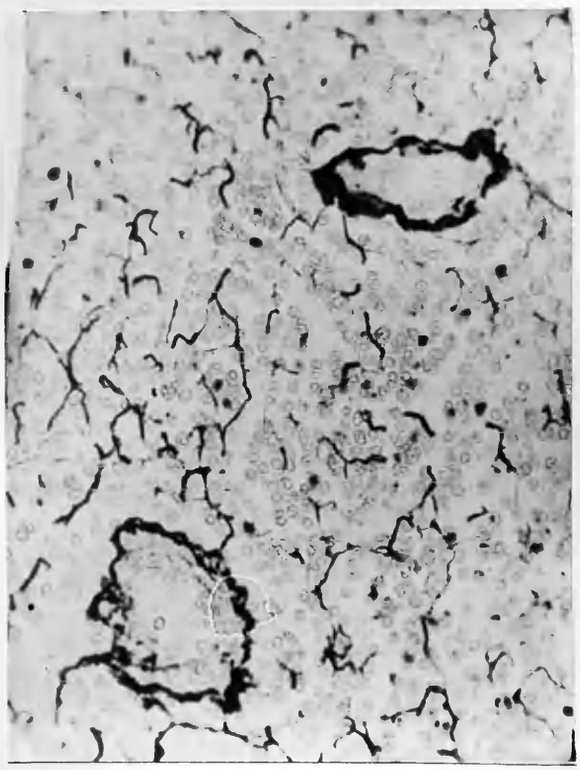


Fig.139. 782. Neoplastic Reticulosis. Gland showing scanty reticulin.
Silver impregnation. × 400.

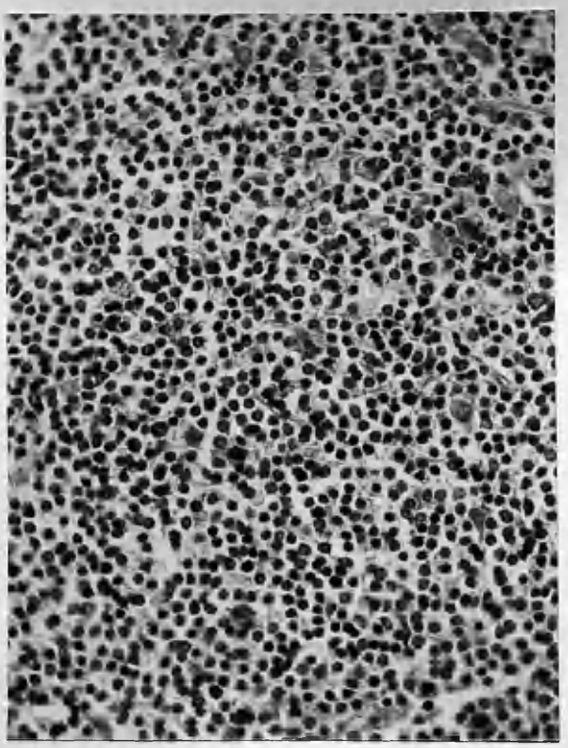


Fig. 140. 778. Neoplastic Reticulosis. Gland. Resembles 782 but more large cells are present.
H.& E. × 400.

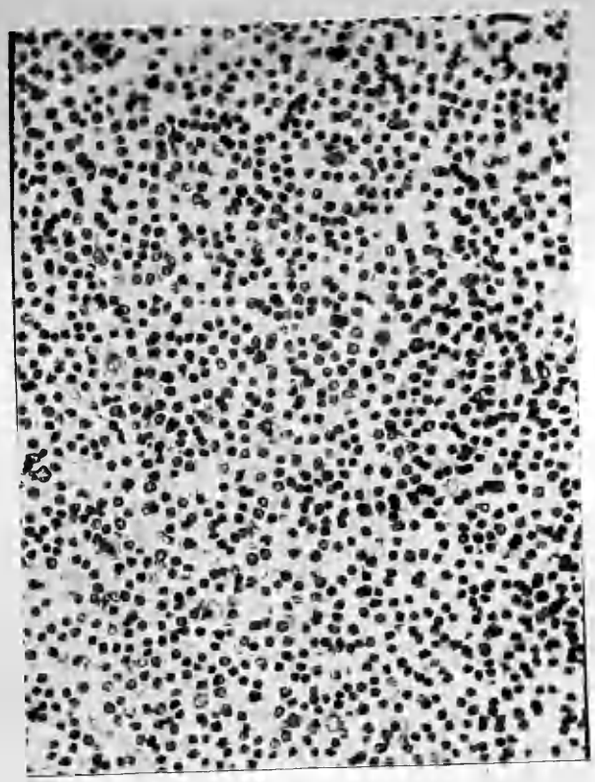


Fig.141. 778. Neoplastic Reticulosis. Gland shows almost no reticulin.
Silver impregnation. × 400.

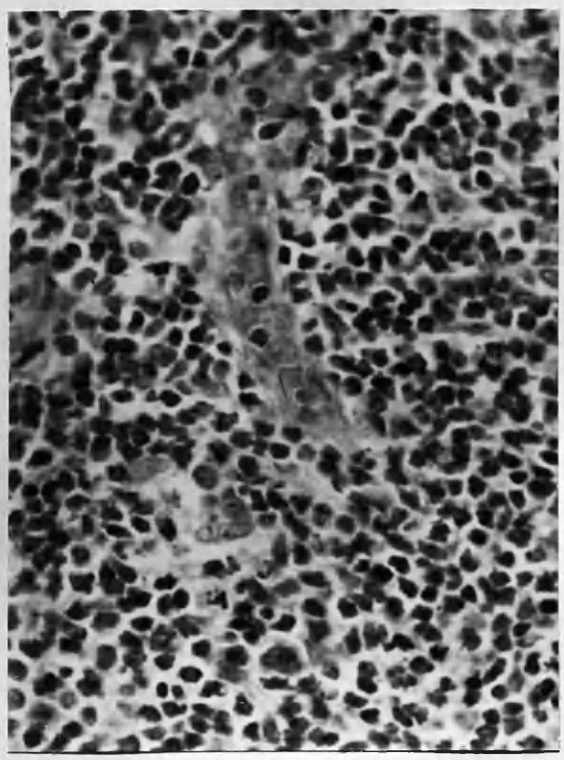


Fig.142. Neoplastic Reticulosis. Gland showing lack of uniformity of cells.
H.& E. × 500.

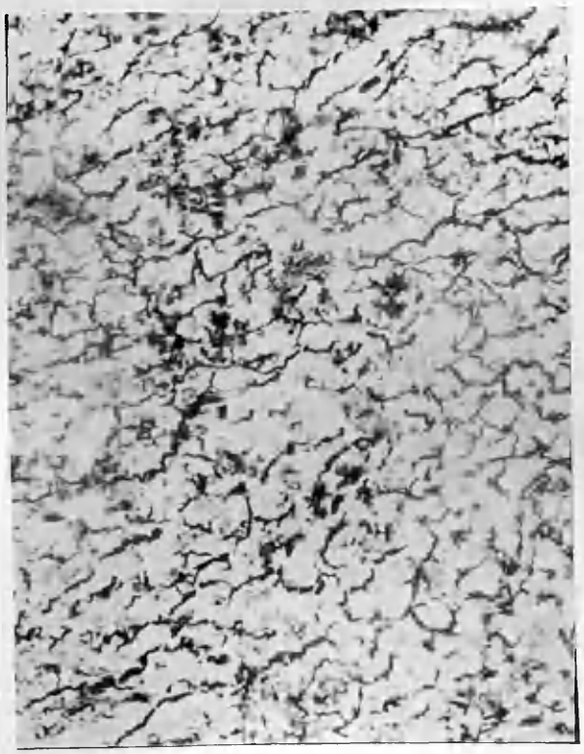


Fig.143. 800. Neoplastic Reticulosis. Gland showing fairly copious reticulin.
Silver impregnation. × 500.

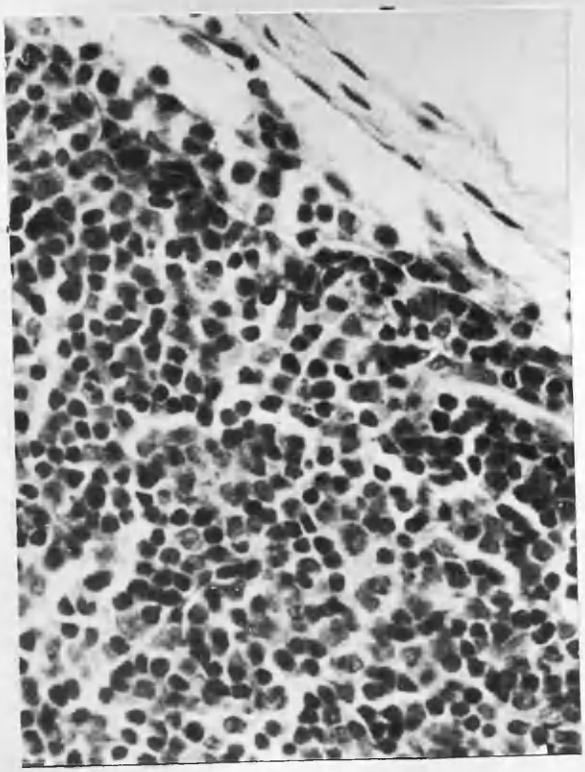


Fig. 144.Afferent Sinus at 12 hrs. Few cells in sinus. Cells of cortex mainly lymphocytes. H.& E. × 500.

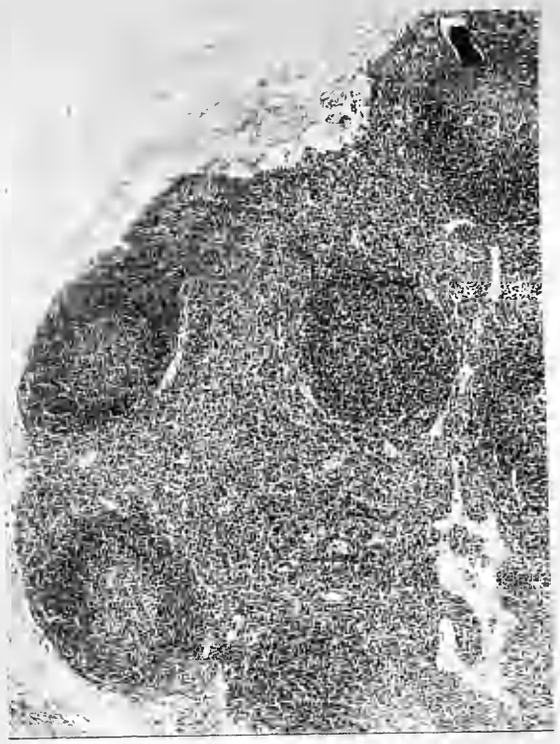


Fig. 145. Gland at 36 hrs. Cortex shows well- defined follicles. cf. follicular hyperplasia of reactive type. H.& E.× 75.

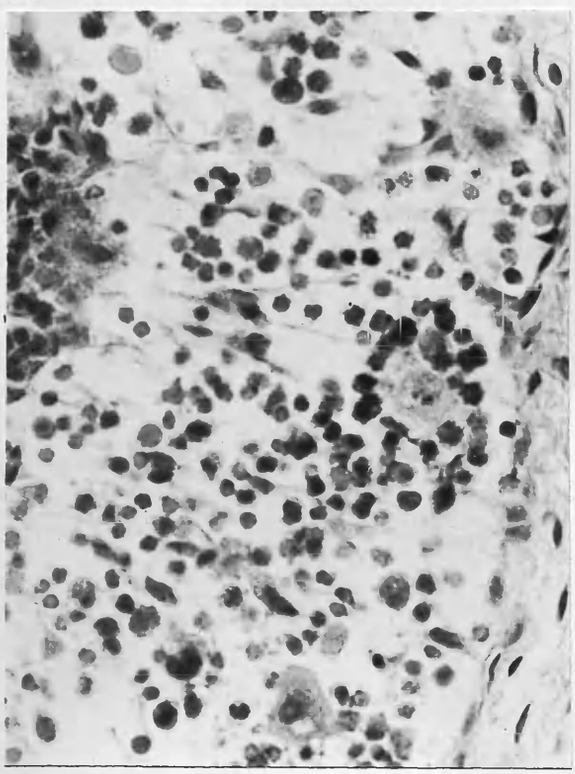


Fig.146. Afferent Sinus at 36 hrs. Macrophages, reticulum cells and lymphocytes also intermediate cell ? monocytes. H.& E. × 500.

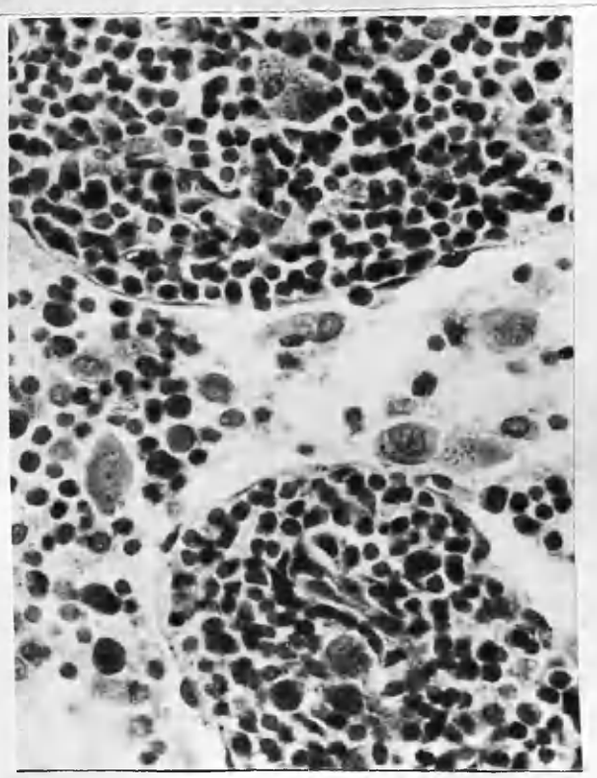


Fig. 147.Medullaru Sinus at 36 hrs. Hyperplastic reticulum cells in medullary cords. Macrophages free in sinus. Slight swelling of sinus endothelium. H.& E. × 500.

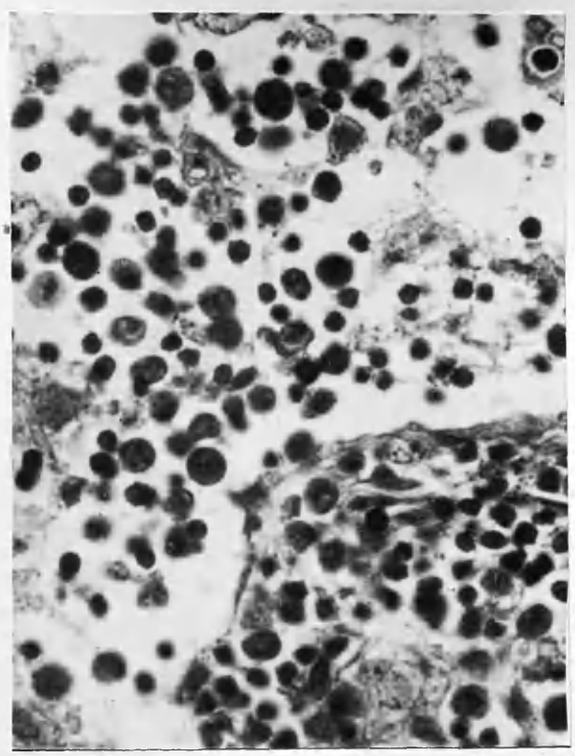


Fig.148.Medullary Sinus at 60 hrs.
Many ?monocytes in sinus and in cords.
H.& E. × 500.

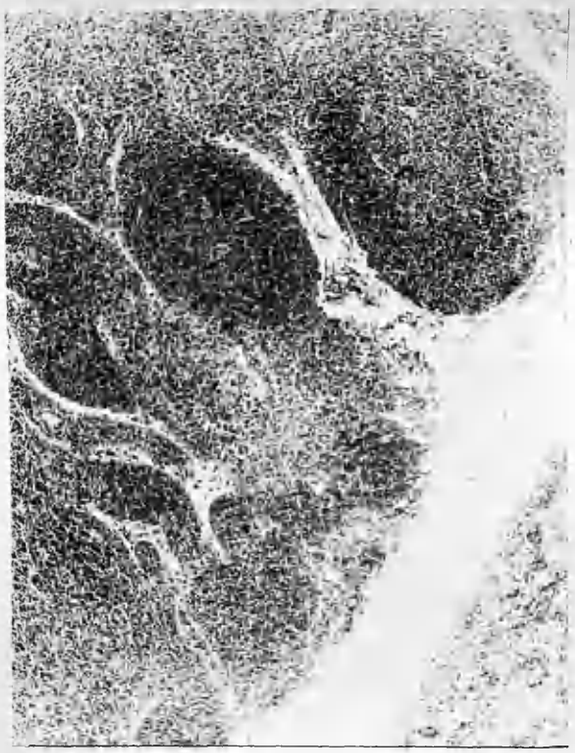


Fig.149. Gland at 60 hrs.
Cortical follicles are becoming less distinct.
H.& E. × 75.

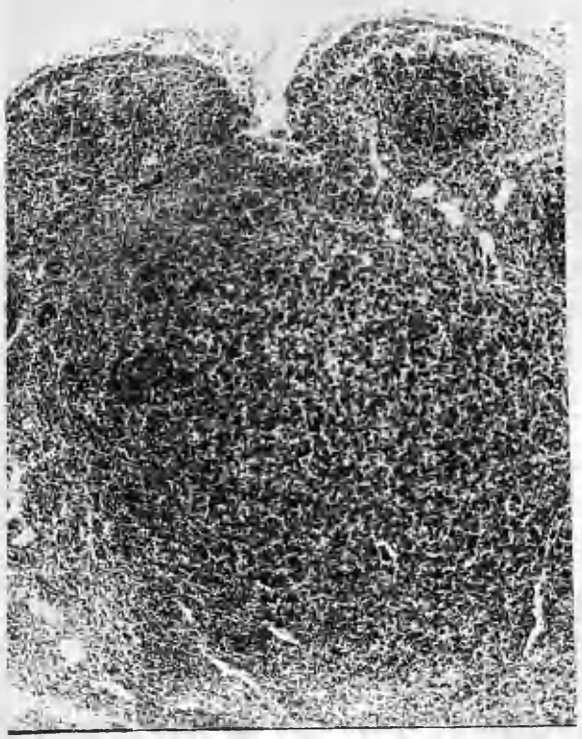


Fig.150. Gland at 72 hrs.
Afferent sinus is cellular.
No definite follicles in cortex.
H.& E. × 100.

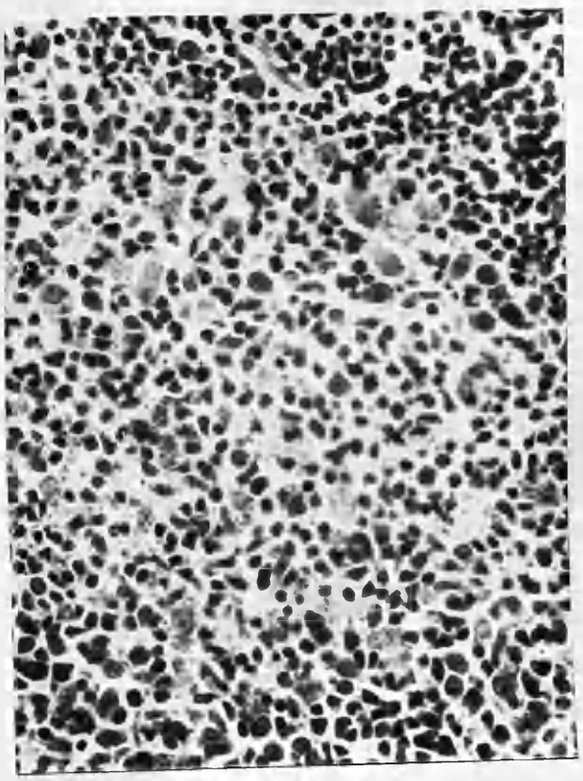


Fig. 151. Gland at 72 hrs. Area of cortex showing hyperplastic reticulum cells.
H.& E. × 400.

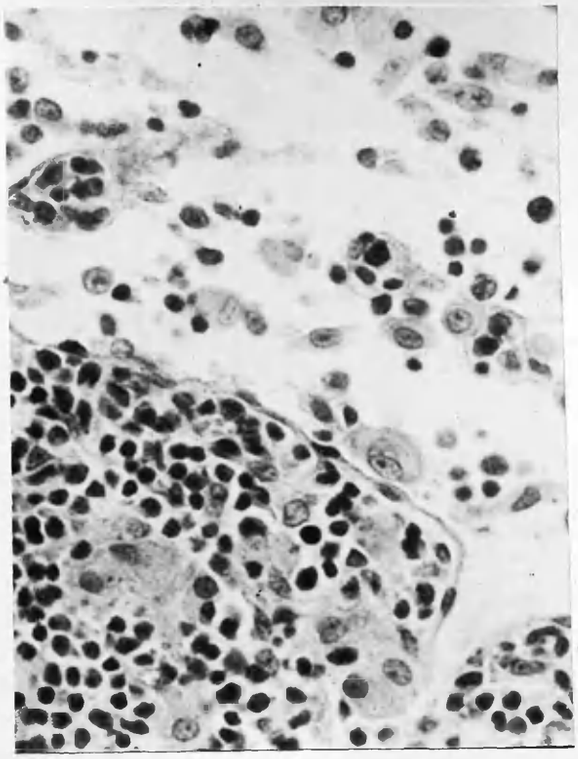


Fig. 152.Medullary sinus at 72hrs. Macrophages,some free in sinus smme fixed in cords. Tending to form plaques. Other cells mainly lymphocytes. H.& E.× 500.

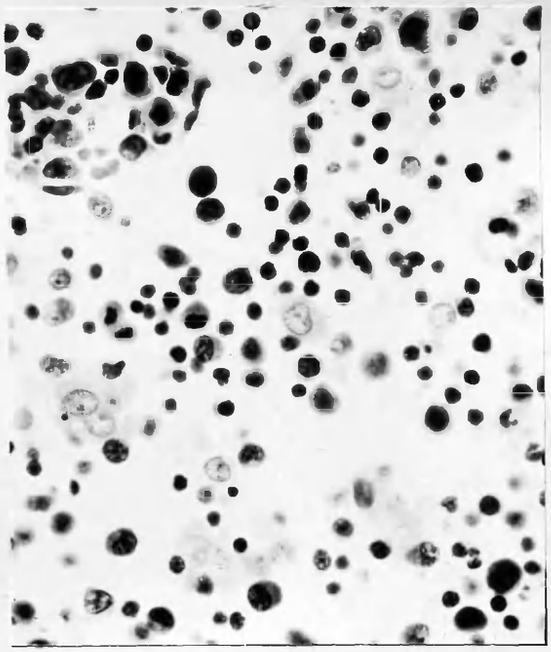


Fig.153.Medullary sinus at 72 hrs. Pale macrophages,lymphocytes and intermediate mononuclear cells ?monocytes.
H.& E. × 500.

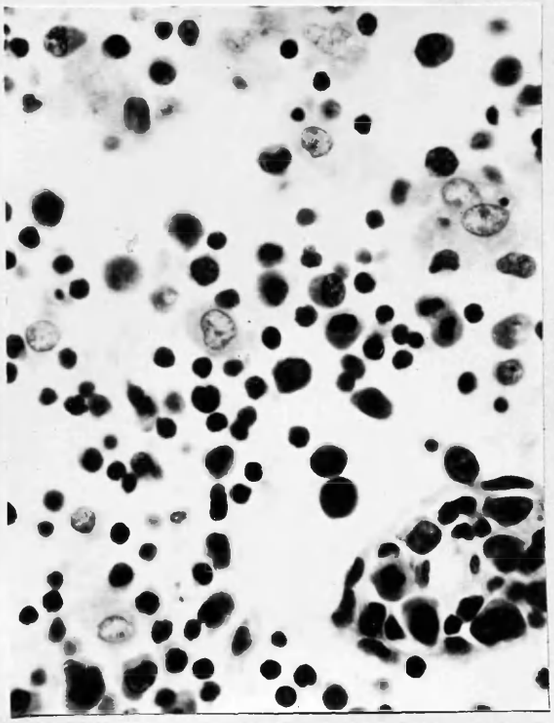


Fig.154.Medullary sinus at 72 hrs. Same types of cell as in Fig. 153. Some ?monocytes are also present in the cords.
H.& E. X 600.

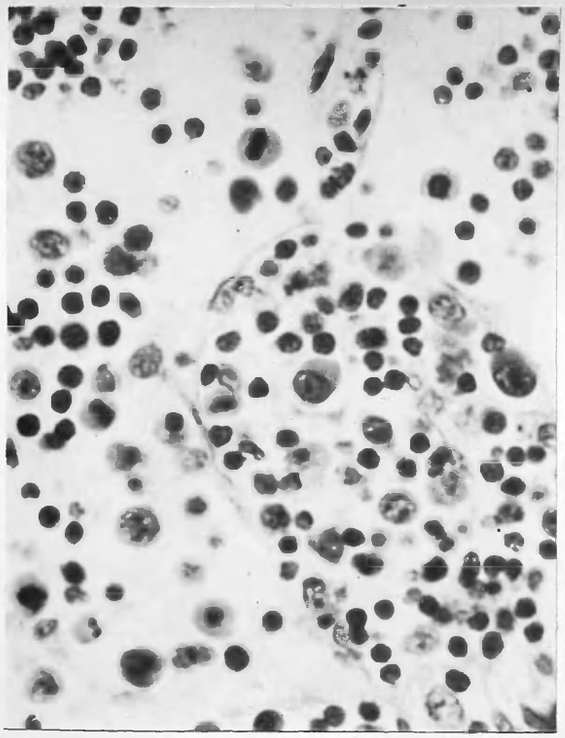


Fig.155.Medullary sinus at 120hrs. Cells mainly of monocytic type in sinus and in cords. Some such cell are undergoing mitosis.
H.& E. × 600.

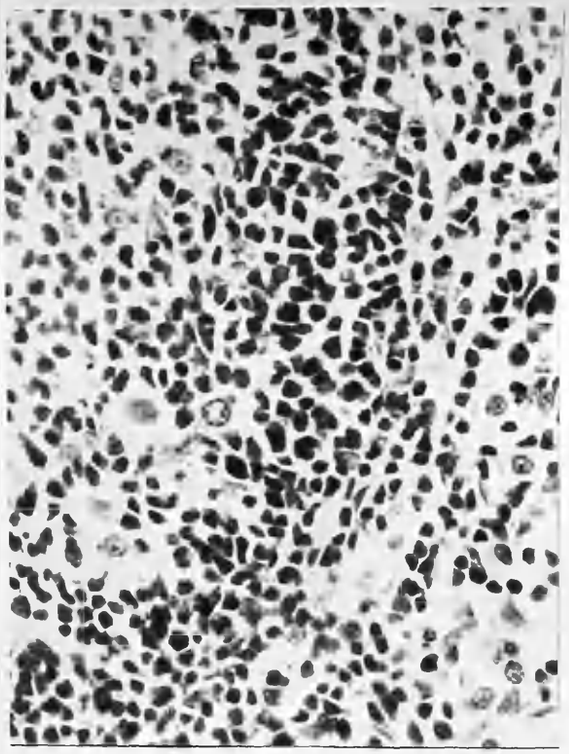


Fig.156. Gland at 144 hrs. Hyperplastic reticulum cells among lymphocytes of cortex.
H.& E. × 300.

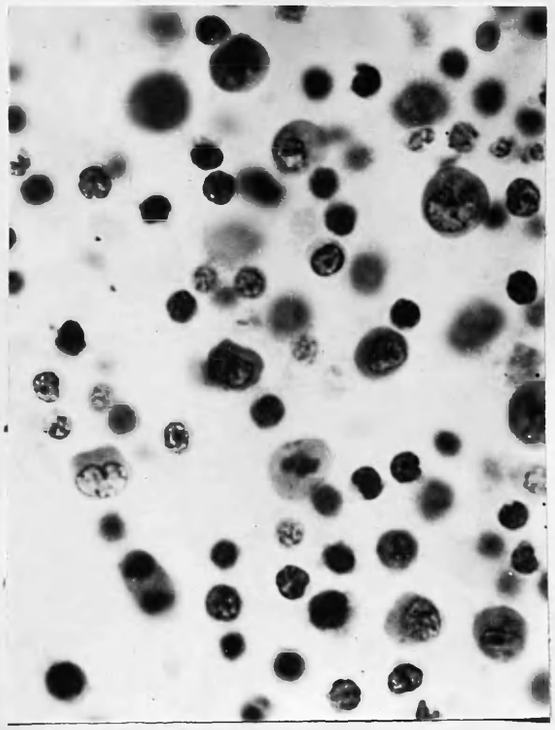


Fig.157.Medullary Sinus at 144 hrs Cells mainly of monocytic type. No macrophages. Mitoses frequent.
H.& E. × 600.

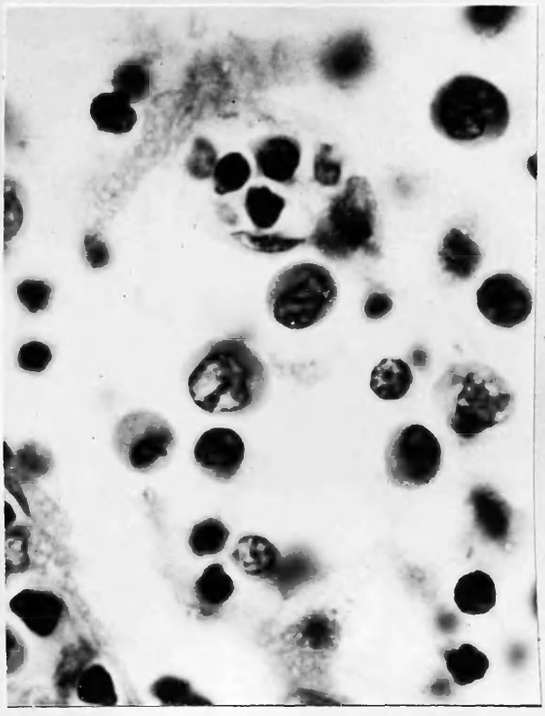


Fig.158.Medullary Sinus at 144 hrs Similar cells to those in Fig.157
H.& E. × 700.

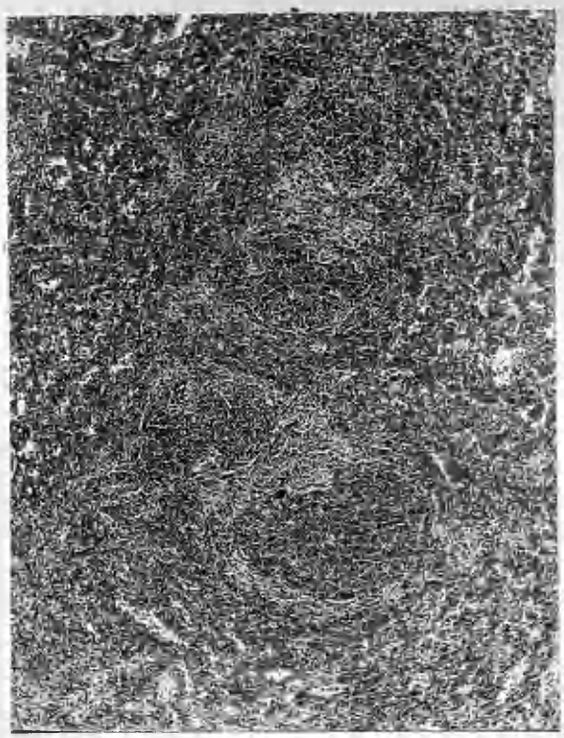


Fig.159. Spleen at 12 hrs.
Malpighian bodies are fairly distinct from the red pulp.
H.& E. × 75.

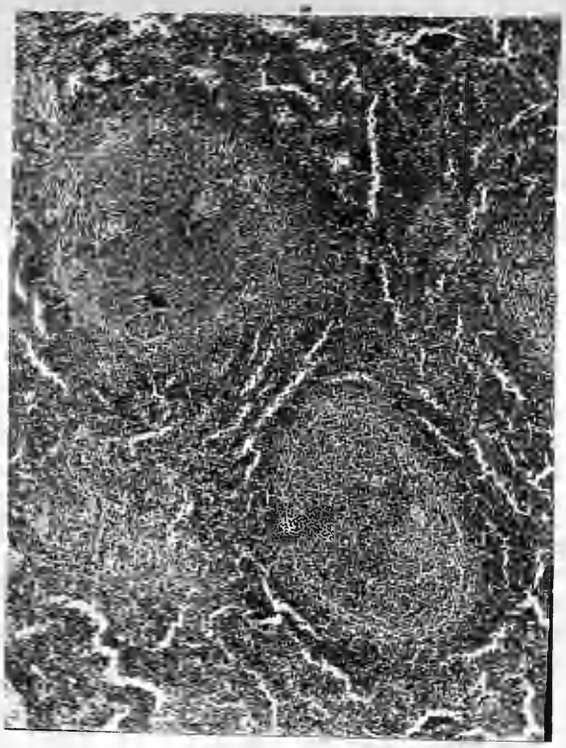


Fig. 160. Spleen at 24 hrs.
Malpighian bodies are well-define
H.& E. × 75.

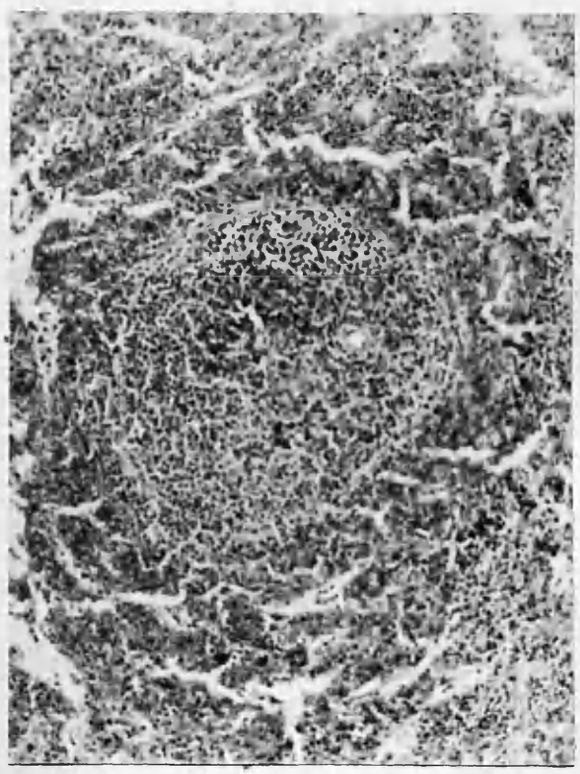


Fig.161. Spleen at 36 hrs.
Malpighian body rather less distinctly defined.
H.& E. × 100.

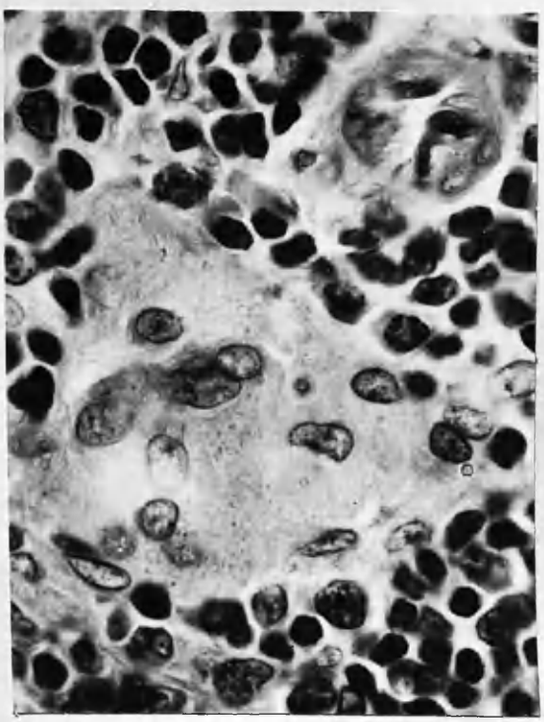


Fig.162. Spleen at 36 hrs.
Malpighian body showing syncytial arrangement of reticulum cells.
H.& E. × 1000.

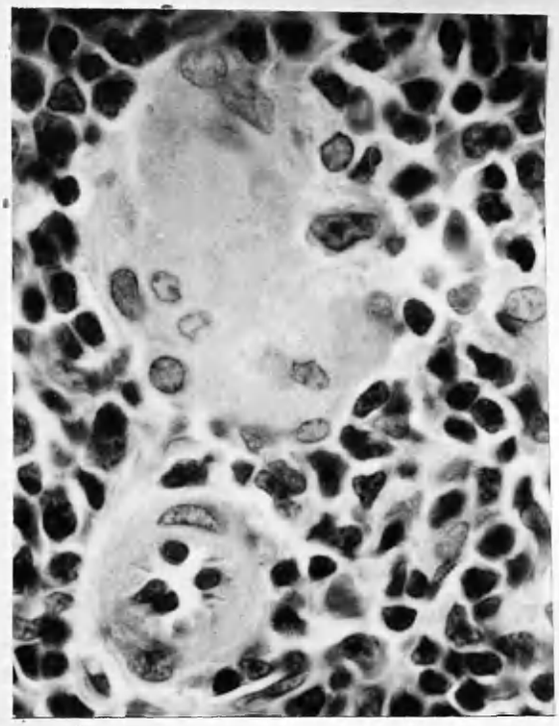


Fig.163. Spleen at 36 hrs.
Malpighian body showing
syncytial arrangement of
reticulum cells.
H.& E. × 1000.

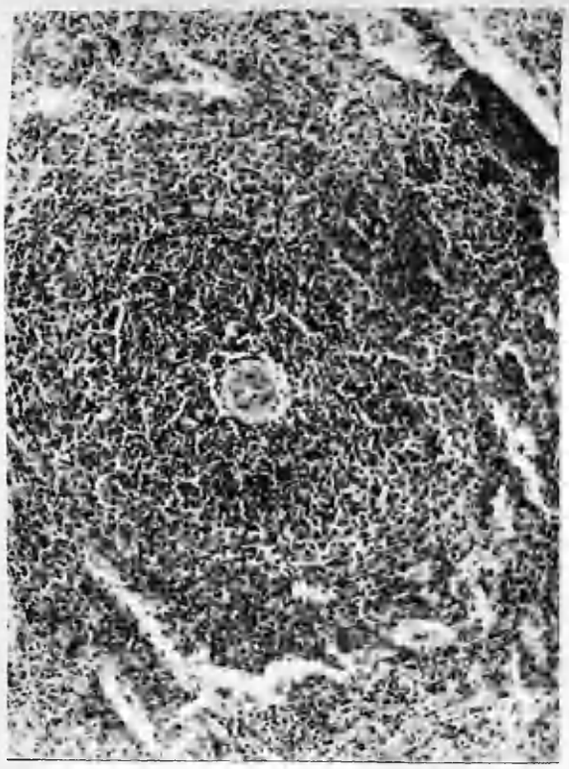


Fig.164. Spleen at 60 hrs.
Malpighian body not clearly
defined from red pulp.
H.& E. × 100.

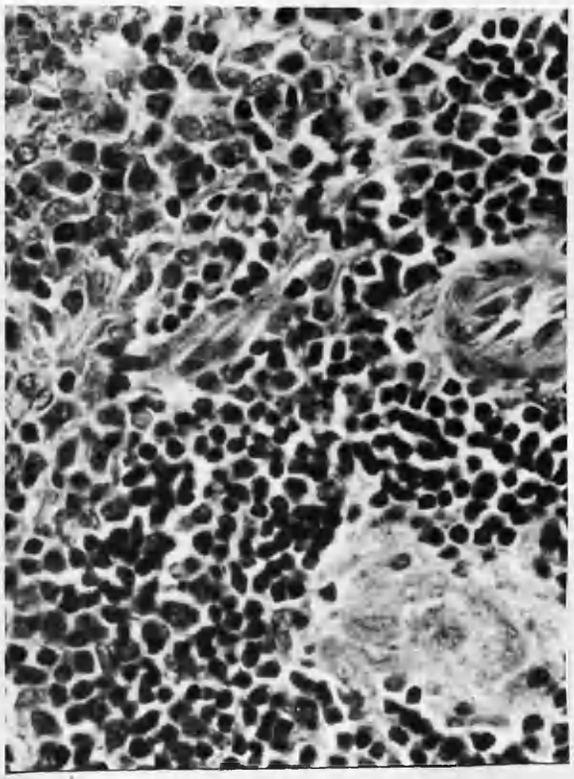


Fig.165. Spleen at 60 hrs.
Plaque of reticulum cells in
Malpighian body also hyperplasia
of reticulum cells around its edge
H.& E. × 500.

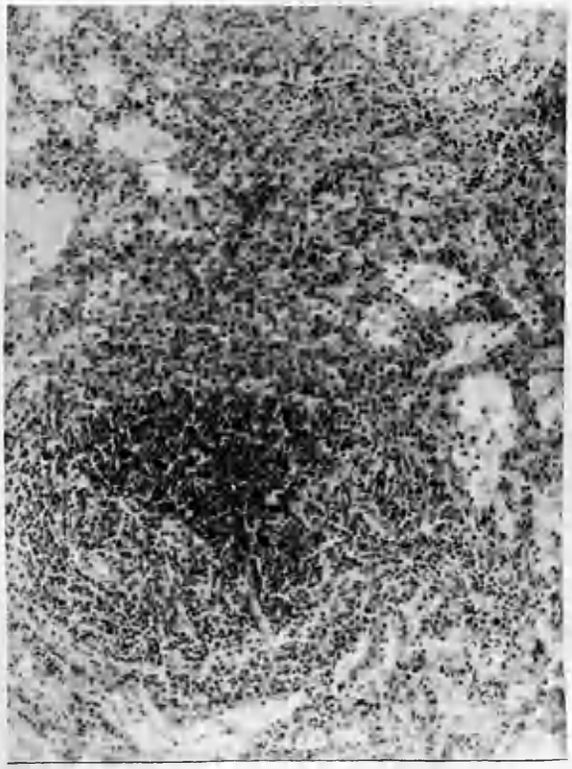


Fig.166. Spleen at 72 hrs.
Malpighian body small, irregular
and ill-defined. Great cellularity
of red pulp.
H.& E. × 100.

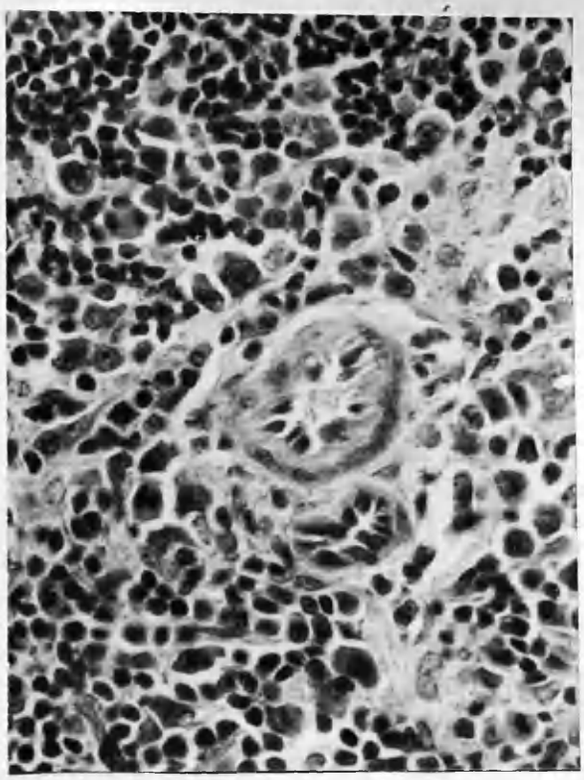


Fig.167. Spleen at 72 hrs. Malpighian body with diverse cellularity. Many large mononuclear cells fixed and free. Mitoses and plaques. H.& E. × 500.

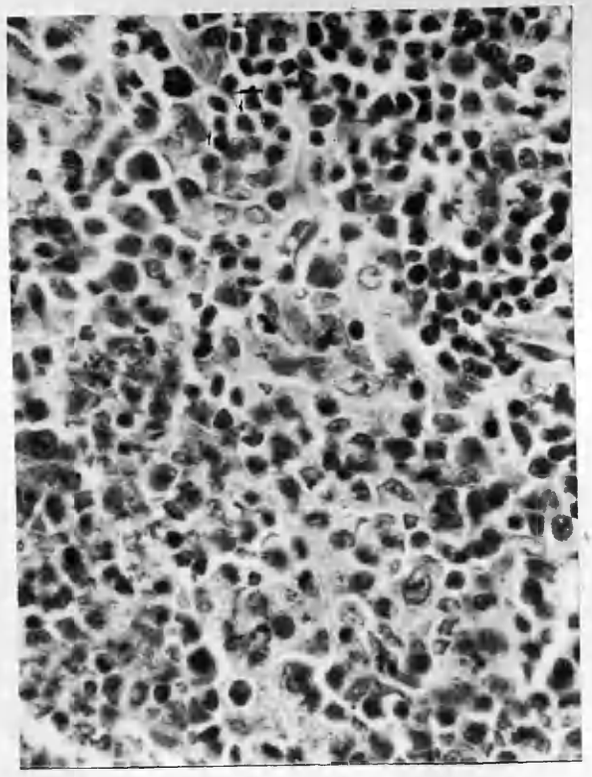


Fig.168. Spleen at 72 hrs. Edge of Malpighian body. Hyperplastic reticulum cells merging with those of pulp(left). H.& E. × 500.

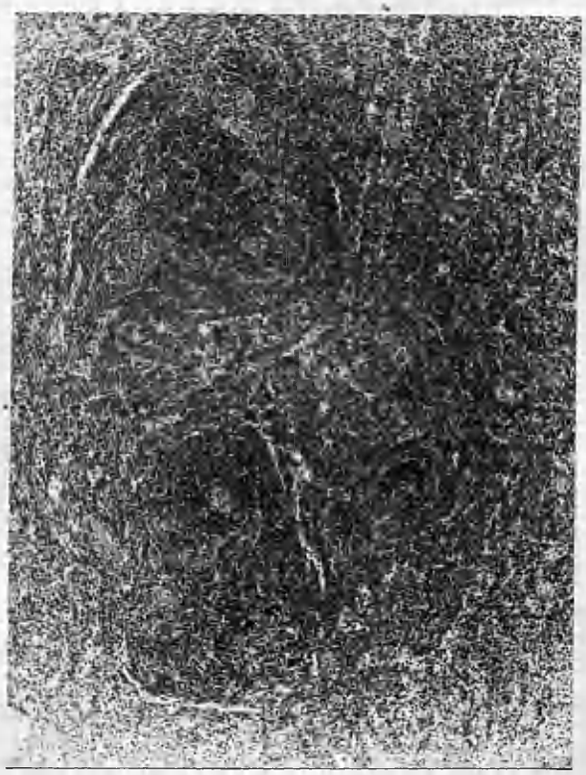


Fig.169. Spleen at 120 hrs. Malpighian bodies not well defined. Pulp very cellular. H.& E. × 75.

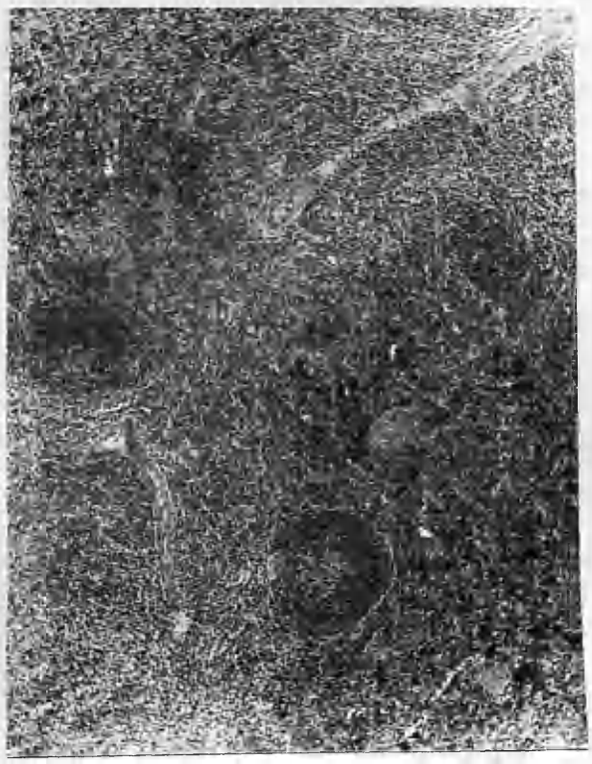


Fig. 170. Spleen at 144 hrs. Malpighian bodies small but more compact. Pulp very cellular. H.& E. × 75.

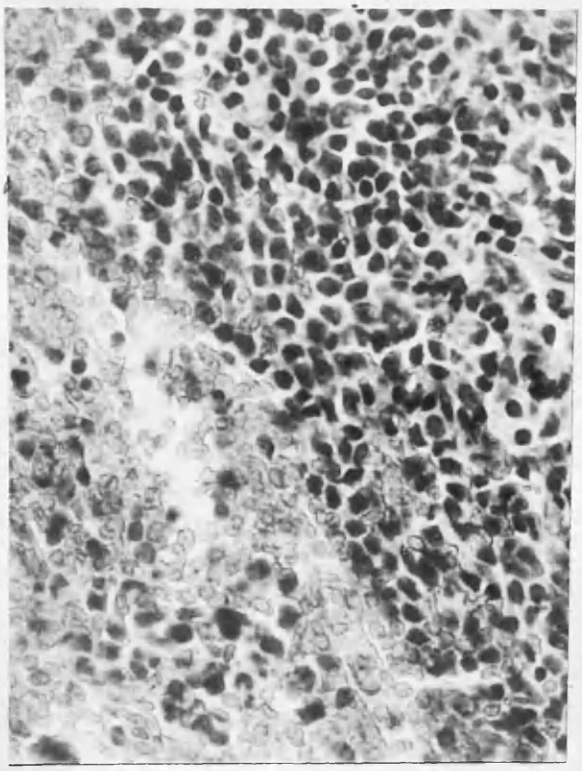


Fig.171. Spleen at 144 hrs. Edge of Malpighian body fairly clearly defined. More blood in pulp than previously.
H.& E. × 500.

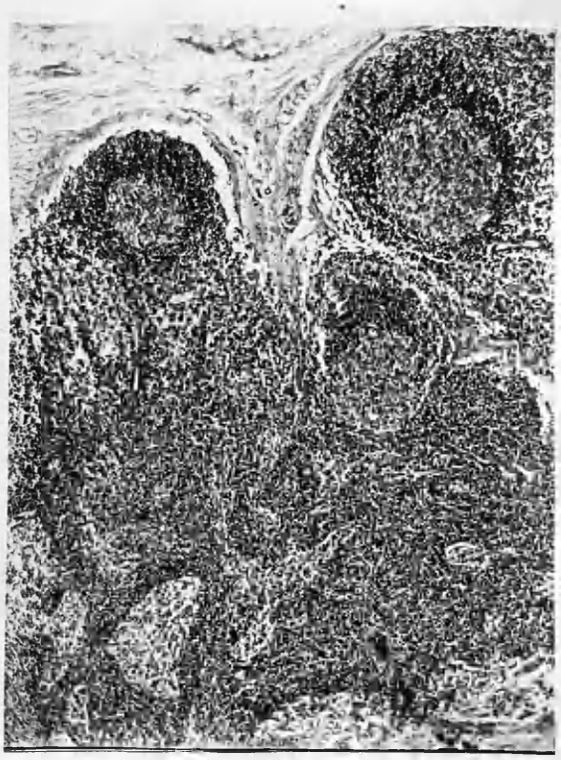


Fig.172. Gland from a case of glandular fever, showing reactive follicular hyperplasia and sinus catarrh.
H.& E. × 100.