The Pathology of Malignant Histiocytoma (Reticuloendothelioma) of the Liver in Mice

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INTRODUCTION

Within recent years workers at the Roscoe B. Jackson Memorial laboratory have made frequent reference to reticuloendothelioma of the liver in mice (4), the growths occurring with a relatively high frequency in the C57 black strain (11). Representatives of this strain have been under observation here since 1934, but until 1940 only one growth of this type had been seen in more than a hundred autopsies on mice over 12 months old; since that date, however, they have become relatively common, the incidence in mice over 18 months of age being now of the order of 15 to 20 per cent, whilst sporadic cases have occurred in those of other strains. Apart from the spontaneous cases in the C57 strain, some have been induced precociously by the cutaneous application of 9,10-dimethyl-1,2-benzanthracene or methylcholanthrene. Details of this work will be published separately, but so far as the dimethyl compound is concerned it appears that a short course of painting with a 0.25 per cent solution is more effective in the induction of leukoses than is more intensive dosage.

The sudden change in the spontaneous incidence of these growths is probably associated with changes in diet necessitated by the war. During the same period hepatomas appear to have become rare in the CBA strain, as have certain renal lesions in the C57 strain. The principal modification was a change from Purina fox chow to Thorley's rat biscuits. In other respects it was not possible to keep the diet constant.

MATERIALS AND METHODS

This paper is based on a study of 11 spontaneous and 10 induced cases, 2 of the latter having been transplanted; these will be referred to as H.R.1 and H.R.2 respectively.

Materials for sections were fixed in neutral formol saline and stained with hemalum and eosin. Whenever possible impression-smears were made of the liver, and of other organs if the gross morbid anatomy appeared to justify it. Blood was generally obtained from the heart and from the tail. Blood and impression-smears were stained after air drying in a 5 or 10 per cent solution of Gurr's improved Giemsa stain buffered at pH 6.4 or 7.0. Blood and liver smears were usually well stained after 5 to 10 minutes at either pH; other tissues needed much longer, up to 2 hours in some cases, and it was found preferable to use the stronger solution at pH 7.0 in such cases.

"Normal" histiocytes were studied in sections and smears of inflamed lymph nodes, in the livers of mice with hepatitis, and in tumor-bearing mice with extra-medullary myelopoiesis.

Transplantation was performed with liver emulsions, and except where stated to the contrary the emulsion was injected into the peritoneal cavity; the dose varied from about 1 to 6 million cells.

RESULTS

Morphological variations in nonmalignant histiocytes.—As seen in sections, murine histiocytes are usually somewhat darker than those seen in inflamed human lymph nodes, and in addition a nucleolus is less often seen in the former species; otherwise they resemble one another closely. A comparative study of the appearance in smears is being published elsewhere (7); here attention will be confined to the murine cells.

The histiocyte is most easily differentiated from the circulating leukocytes by means of its cytoplasm. With Romanowsky stains this is generally sky blue, and of a structure that might be interpreted as finely granular or as a foam with the stain adsorbed at the interfaces. Occasionally the cytoplasm is chromophobic, the stain being confined to the cell membrane. Cells with a dull blue cytoplasm are probably degenerate but an increased basophilism, where the color is a brilliant blue or greenish-blue, is indicative of a left shift. Under these conditions the structure may be coarser than normal, and filamentous bodies may be visible; the latter are almost certainly mitochondrial rods.

1 H.R. = Hepatic reticulosis.
The nucleus is typically round or oval, and the ground color varies in different preparations from pink to deep mauve, with fine basophilic stippling; in addition there are usually one or two knots of chromatin and sometimes one or two chromat threads. The mature cell generally has no visible nucleolus; the presence of such a structure is indicative of immaturity and is commonly accompanied by a modification of nuclear structure towards that commonly associated with blast cells.

It is by no means uncommon to find the nuclear structure resembling that of a lymphocyte. Since the size of the histiocyte may be anything from 6μ to 26μ, it may be impossible to be certain of the identity of any particular cell, unless one is lucky enough to find a dwarf lymphocytoid histiocyte in the act of phagocytosis.

As it is now generally accepted that monocytes and histiocytes represent different functional phases of the same cellular type, it is not surprising to find forms morphologically intermediate between the two stages. However here one should stress, as Bloom (3) has done, that the nuclear differentiation of lymphocytes and monocytes is by no means so easy in mice as in man, and the differentiation of monocyteid and lymphocytoid histiocytes may be arbitrary in certain cases.

THE MORBID ANATOMY OF MALIGNANT HISTIOCYTOMAS

The physical signs shown by a mouse with one of these tumors depends upon the fact that they may have ascites and subcutaneous edema, ascites alone, or hepatic enlargement without either. Cases are rather easy to miss; in the first instance the animal simply appears to be rather fat, whilst in the last it may have extensive pulmonary involvement before abdominal distention has become easily noticeable. Death is sometimes due to hemoptysis, hemorrhage into the peritoneal cavity, and presumably to hepatic insufficiency.

Edema fluid is always clear, whilst ascitic fluid may be clear, turbid, or contain blood.

The liver is enlarged to a variable extent, and in extreme cases may almost reach the pelvis. Its surface is finely granular and often shows yellow areas of infarction.

The spleen may be uniformly enlarged or nodular. In the former case (other than in the transplanted disease) it shows extramedullary myelopoiesis whilst the nodules are metastatic.

The mesenteric lymph nodes are sometimes considerably enlarged, as occasionally is the thymus; the superficial nodes are normal.

The lungs almost invariably have excessive hemorrhagic, edematous areas, but apart from this there are no macroscopic visceral abnormalities.

Morbid histology.—Inspection of early cases gives strong grounds for supposing that the growth is multicentric in origin (Figs. 1, 2), in which respect it resembles the malignant hepatomas and cholangiomas found in man. In this particular case the malignant cells showed exaggerated phagocytic activity, a feature shared by 3 other cases, which made these cells easy to pick out. Some of these hyper-phagocytic cells may be seen singly attached to the sinusoids, whilst there are large accumulations of cells scattered at random throughout the liver. There may be considerable hemorrhage in these areas, and some of the contents may be lost during the preparation of the sections. However, the random distribution of the main foci of proliferation makes the condition easy to differentiate from extramedullary myelopoiesis, which it resembles in macroscopic appearance. In the latter condition the main foci of proliferation are almost invariably round the larger blood vessels and the sinusoids are invaded secondarily from them (Fig. 4). Ultimately the whole liver becomes invaded, with the sinusoids grossly distended, but the larger foci of proliferation usually remain visible. Circulatory disturbances in the organ give rise to the areas of infarction and to the granularity. The latter is produced by distention of the sinusoids, with considerable destruction of the hepatic parenchyma. Hemorrhage may occur from such areas, which appear not unlike an angioma (Fig. 5).

The method of spread may also be seen in sections, including massive invasion of the hepatic veins and embolic invasion of the lymphatics. In the latter case, spread is presumably retrograde to the mesenteric lymph nodes and spleen (Figs. 6 to 9).

The appearance of the malignant cells varies in detail from case to case, and in different areas of the same liver. Cells invading the veins or lymphatics seldom contain much phagocytosed material regardless of the behavior of those in the liver as a whole. In only one case were the cells apparently primitive, and in another grossly aberrant cells were numerous. In all the rest the dominant cell was a mature histiocyte, variation affecting mainly the depth of staining and the degree of phagocytic activity shown.

A puzzling complication is the occurrence of considerable myeloid infiltration in certain cases; here reliance must be placed upon the behavior of the histiocytes and on the merits of the case as a whole (Fig. 6).

The spleen sometimes shows nodular accumulations of histiocytes, which may tend to invade the pulp. In the lymph nodes the malignant cells may be confined to the sinusoids, but if the pulp is invaded they become packed together and the appearance is that of a spindle-cell sarcoma. This appearance was first seen in an induced case (the origin of H.R.1), and it was natu-
Figs. 1 and 2.—Fact of proliferation in early spontaneous case of malignant histiocytoma with hyper-phagocytic cells. Note that they have no tendency to be related to the larger blood vessels. The focus in Fig. 2 is far removed from those shown in here. Mag. X 100.

Fig. 3.—High power view showing hyper-phagocytic cells. Mag. X 600.

Fig. 4.—Extramedullary myelopoiesis in liver of mouse with induced skin cancer. Note concentration of areas of proliferation around the larger blood vessels. Mag. X 100.
rally thought that one was dealing with multiple induction (Fig. 10). However, since that date a spindle cell area has been observed in the liver in one case, and the transplantation experiments have made it certain that histiocytic tumors may assume this appearance. If spindle cell areas are smeared the cells spread out, very few maintaining their original shape (Fig. 11). It is of interest to record a male patient described by Baumgarten (1), apparently with monocytic leukemia, who had generalized spindle cell sarcomas of the lymph nodes.

In other viscera metastases are usually visible as intra-vascular emboli. Their presence in the lungs is invariable in all mice that die of the disease, and is often accompanied by hemorrhage into the alveoli. They may be found in almost any viscus, but their distribution is inconstant.

**Blood picture.**—In most cases the only feature in common between blood from the tail and that from the heart are indications of anemia.

(a) *Tail blood.*—The picture here is extremely variable. Quantitatively the white count may be normal. One usually sees a certain number of mononuclears that one suspects of malignancy, and a prolonged search may reveal an obviously malignant histiocyte. A polymorphonuclear leukocytosis is by no means uncommon, and this may be accompanied by a monocytosis. For example, in one case there were 15,000 white cells, of which 7,500 were polymorphonuclears, 2,500 lymphocytes, and 5,000 "monocytes." Some of the latter were phagocytic and others were in mitosis. In 3 cases a true monocytic leukemia occurred.

(b) *Heart's blood.*—Blood obtained by cardiac puncture at autopsy, and perhaps in life, generally comes from the right ventricle. Fekete (6) found that in normal mice the leukocyte count was generally lower in the heart's blood than in blood from the tail. This is not true of a number of pathological conditions. Here it is always possible to find numbers of histiocytes, some lying singly whilst others are in embolic clumps (Fig. 12). Histogenous mast cells may be present, and young myeloid cells may be more frequent than in the tail blood.

The appearance of liver smears.—There is no criterion that will enable one to identify a given cell as certainly malignant; the picture must be judged as a whole. However a brilliantly staining cytoplasm, a coarse structure, and hyper-phagocytosis are all strongly indicative. In typical cases the smear will contain very little besides histiocytes and the remnants of hepatic cells, the isolated nuclei of which are lephtochromatic with coarse chromatin aggregations and several nucleoli; they might be mistaken for primitive or aberrant histiocytic nuclei. The cytoplasm, when present, is deeply basophilic and of a spongy texture.

Difficulty in diagnosis may arise if there is an accompanying myelosis, when inflammatory conditions may be closely mimicked. The above criteria will be found useful, but in addition one should look for large masses of histiocytes. Syncytial masses of these cells may occur in infections, but not to such an extent as in neoplastic conditions.

The histiocytes are somewhat pleomorphic and a few histioblasts may be present, but as a general rule the cells are mature and conform on the whole to a given type. A few multinucleate cells may be generally found, and these are often of the Reed-Sternberg binucleate type. In one case only were very aberrant hyper-phagocytic giant cells numerous. The original cases of H.R.1 and H.R.2 are good examples of the general run. In the first the bulk of the nuclei were of monocytoid or lymphocytoid type, the cytoplasm being typically histiocytic and brilliantly basophilic (Fig. 13). In H.R.2 there was considerable myeloid reaction, and considerable inflammatory change affecting the larger blood vessels. The histiocytes were fairly normal in appearance, but were hyper-phagocytic (Figs. 6, 7, 14). The latter, in conjunction with the presence of emboli in the heart's blood, determined the diagnosis and enabled transplantation to be undertaken with confidence.

**Transplantation experiments.** (a) *H.R.1.*—Table I shows the general modifications undergone by H.R.1 following routine intraperitoneal inoculations for the first 20 transfers. Reference to the results of subcutaneous transfers made at the second, fourth, fifth, tenth, and 11th passages will be made later. Since the 20th transfer all inoculations have been subcutaneous.

It will be seen that the tumor underwent 3 morphological phases and 4 phases in growth rate.

The gross morbid anatomy during the first 2 transfers was very similar to that of a spontaneous case, there being very little evidence of cellular proliferation in the peritoneal cavity or mesenteries and the liver being enlarged and diffusely infiltrated. The cells were perhaps somewhat larger than in the original case, and lymphocytoid forms were less numerous.

From the third to the 15th transfer there was considerable cellular proliferation in the mesenteries, with large aggregations of malignant cells in the pelvis and on the surfaces of the viscera. The intestines tended to be matted together, the whole picture suggesting a plastic peritonitis. The liver generally showed numerous discrete metastatic nodules, although occasionally it was diffusely infiltrated.

Histologically the great bulk of the extrahepatic deposits were spindle cell sarcomas, with occasional giant cells that were often of the Langhans type. Some deposits were round cell sarcomas of the "reticulum" cell type. Spindle cell areas were rare in the liver.
Fig. 5.—Dilatation of sinusoids in spontaneous case. Note angiomatosus appearance, but (top right) that one of the sinusoids communicates with a hepatic vein. Same case as Fig. 12. Mag. × 100.

Fig. 6.—Induced case, origin of H.R.2. Extramedullary myelopoiesis, plus malignant emboli in veins. Mag. × 100.

Fig. 7.—High power view of malignant emboli in origin of H.R.2. Compare with Fig. 22. Mag. × 600.

Fig. 8.—Induced case, origin of H.R.1. Note absence of myelopoiesis, emboli in lymphatics (bottom left) and vein (top right). Mag. × 100.
Fig. 7.--High power view of lymphatic embolus. Compare with Figs. 10, 15, 16, and 20. Mag. X 600.

Fig. 10.--Spindle cell metastasis in mesenteric lymph node of case above. Mag. X 100.

Fig. 11.--Smear from spindle cell metastasis of transplanted case (H.R.I. thymus transfer). This is the usual appearance: few cells retain the spindle form. Same case as Figs. 15 and 16. Mag. X 600.

Fig. 12.--Malignant embolus in heart's blood of spontaneous case. Mag. X 600.
Fig. 13. Liver smear from origin of H.R.1. Cells tend to have dark "lymphocytic" nuclei. Some were phagocytic. Mag. \( \times 600 \).

Fig. 14.—Liver smear, origin of H.R.2. Histiocytes fairly normal in appearance. Several contain ingested red cells, including one small lymphocytic cell near center. Mag. \( \times 600 \).

Fig. 15.—Spindle cell sarcoma, subcutaneous implant, H.R.1, tooth transfer (see Fig. 11). Mag. \( \times 100 \).

Fig. 16.—High power view of spindle cell tumor. Mag. \( \times 600 \).
Generally the histiocytes were large and bloated, but of epithelioid or "reticulum" cell form. Multinucleate cells were fairly numerous. There was a considerable tendency towards a diffuse infiltration of the sinusoids, the metastatic nodules being less discrete than appeared macroscopically (Figs. 15-19).

Embolic metastases were always seen in the lungs, and in late cases in almost every organ in the body.

In liver smears it could be seen that a number of the cells were extremely aberrant. There was considerable anisocytosis; the nuclei were somewhat dark and generally contained 3 or 4 nucleoli, around which were coarse aggregations of chromatin. Multinucleate cells and cells with very bizarre nuclei were far commoner than one would deduce from a study of sections.

Diffuse infiltration in the peritoneal tissues disappeared completely. There was gross enlargement of the liver and spleen, and generalized enlargement of the lymph nodes. The cellular picture was that of a blast cell leukemia, and one who did not know the history of the case might consider it a lymphoblastic leukemia. A number of the cells were hypoploid, and one with only 16 chromosomes was seen (Figs. 20, 21).

Differentiation can still occur to some extent (Fig. 21). It occasionally may be seen in the diffuse deposit one may get following subcutaneous transmission, where many bizarre forms may be seen. In liver smears small monocytoid histiocytes seem to occur fairly regularly. Transitions between these and the histioblasts can be made out. Differentiation perhaps occurs following an abortive mitosis. The kidney shaped nucleus being constituted round the metaphase chromosomes (9).

The cell count in blood from the tail is as a rule grossly raised only towards the end of the disease, when it may be 100,000 or more, but a few primitive cells may be generally found much earlier.

The dose has been reduced to about 100,000 cells, administered subcutaneously, in an effort to prolong life and economize in mice. However, in the most recent transfers the disease seems to have gained slightly in virulence and generally kills in from 14 to 30 days.

### Table I: The Changes Undergone by H.R.I Following Intraperitoneal Inoculation

<table>
<thead>
<tr>
<th>Transfer no.</th>
<th>No. of mice</th>
<th>Days of death</th>
<th>Anatomical notes</th>
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<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>K35,36, D.35,39(2),52.</td>
<td>Similar to spontaneous case.</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>K.27,27-33.</td>
<td>Diffuse enlargement of liver.</td>
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<tr>
<td>3-10</td>
<td>50</td>
<td>D.39-95 (Median 61)</td>
<td>Malignant plastic peritonitis. Metastases in liver. Extrahepatic deposits, spindle cell sarcoma.</td>
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<tr>
<td>11-15</td>
<td>20</td>
<td>D.16-48. (Median 26)</td>
<td>As before.</td>
</tr>
<tr>
<td>16 and on.</td>
<td>D.14-30 (Variable, depending on dose and age of mice)</td>
<td>Acute leukemia. Small primitive cells.</td>
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*K* = killed.

*D* = died.

Myelopoiesis in the liver was of sporadic occurrence. At the seventh transfer there was a diffuse infiltration with eosinophils, which had not been seen before and has not been observed since.

The blood picture was variable, probably depending in part on the stage of the disease at which an examination was made. A true leukemia was never seen, but the tail blood might contain as many as 5,000 "monocytes" per cu. mm. out of a total of 15,000 leukocytes.

The results of subcutaneous inoculation were very unreliable; in some cases death occurred as rapidly as with the alternative route, but 5 mice inoculated at the tenth transfer on January 2, 1945, are still symptom-free more than 1 year later. Prior to the tenth transfer the subcutaneous deposit was often invisible during life, and was never more than a minute papule. The regional lymph nodes were very slightly enlarged, and on section the malignant cells seemed concentrated in the sinuses. They were large and well spread out, whilst the small subcutaneous papule might be spindle celled. The picture is very reminiscent of that described by Parsons (1938), which seemed to indicate possible tumor induction in the lymph node by some extracellular agent. The liver was greatly enlarged, and the ultimate course of the disease was little different from that seen following intraperitoneal inoculation. At the tenth transfer the general picture was similar, but the subcutaneous tumors were about 1.0 cm. in diameter.

The drop in growth rate that occurred subsequent to the second transfer may not be entirely due to a diminished rate of cell division; involvement of the peritoneum would tend to produce symptoms less rapidly than when cellular proliferation was occurring in the liver. The acceleration of growth that occurred at the 11th transfer was not accompanied by any obvious anatomical change. At the 16th transfer a sudden and dramatic transformation occurred when the growth took on the morphology of acute leukemia.

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*D* = died.
Figs. 17 and 18.—Hepatic metastases from tumor in Figs. 15 and 16. Giant cells were seldom so numerous as this in H.R.1, but were more often abundant in H.R.2. Mag. × 100 and × 600.

Fig. 19.—Hepatic deposit, Hodgkin's disease (human), to compare with Fig. 18. Mag. × 600.

Fig. 20.—Appearance of liver in H.R.1 from 16th transfer on. Compare with Figs. 8, 9, and 17, 18. Mag. × 600.
Fig. 21.—Liver smear, H.R. 1, 16th transfer. Cells so dark that nuclei do not show up well. Two aberrant histiocytes may be seen; most of the cells look like lymphoblasts. Blood was leukemic. Mag. X 600.

Fig. 22.—Liver of H.R.2, sixth transfer. Note that cells have morphology of "reticular" or germinal center cell, with vesicular nucleus and prominent nucleolus. In smears many show mature histiocytic cytoplasm. Compare Figs. 7 and 23. Mag. X 600.

Fig. 23.—Smear from liver of H.R.2, sixth transfer. Difference between histioclastic and mature cytoplasm readily appreciated by comparing dark cell at left center with those of central clump. Nucleoli can be made out in most of latter; they are particularly prominent in large binucleate cell at right bottom. Compare Figs. 13 and 14. Mag. X 600.

Fig. 24.—Smear from liver, H.R.2, 13th transfer. Reed-Sternberg giant cell, with great anisocytosis amongst other histiocytes. Mag. X 600.
17 days. It still remains specific for the C57 black strain.

(b) H.R.2.—Table II shows that with this tumor there was a progressive increase in virulence for the first 4 transfers; thereafter the behavior remained fairly constant until the tenth, when the growth rate fell and has since remained low but variable, like the middle period of H.R.1.

During the first 10 transfers the lesions were mainly concentrated in the liver, which was generally diffusely enlarged.

In the first 3 transfers there was considerable ascites. At the fourth passage this was diminished, but there was a striking tendency to hemorrhage.

From the 12th transfer onwards there has been a transfer, and there still seemed to be a greater tendency for malignant cells to enter the peripheral circulation than was the case during the middle period of H.R.1.

Histologically the extrahepatic deposits are usually spindle celled, together with numerous giant cells of various types; they are seen more often than with H.R.1.

Subcutaneous inoculations were performed at the third and fourth transfers. The results were anatomically similar to those obtained with H.R.1, but the time of death was even more delayed. Thus following intraperitoneal inoculation at the fourth transfer death occurred between the 24th and 27th days, whilst 3 mice inoculated subcutaneously died between the 87th and 89th days.

**TABLE II: THE CHANGES UNDERGONE BY H.R.2 FOLLOWING INTRAPERITONEAL INOCULATION**

<table>
<thead>
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<th>No. of mice</th>
<th>Days of death</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>K.102(2). D.113(2).119.</td>
<td>Similar to spontaneous case. Progressive left shifts in cells.</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>K.42.49. D.48.49.</td>
<td>Transition gradual to next stages.</td>
</tr>
<tr>
<td>11-17</td>
<td>40</td>
<td>D.37-137. (Median 75).</td>
<td></td>
</tr>
</tbody>
</table>

K = killed. D = died.

malignant plastic peritonitis similar in appearance to that described in H.R.1.

During the first 3 transfers there was considerable diminution in the myelopoiesis compared with the original case, as there was in phagocytic activity. During the period of maximum activity the picture was more that of a round cell sarcoma or an acute blast cell leukemia (Fig. 22). A feature of this period was direct invasion of the thorax by way of the diaphragm, with the formation of deposits on the heart.

Liver smears of the first transfer showed many lymphocytoid and monocyctoid forms. From then until the fourth there was a progressive left shift that was perhaps even more notable at the sixth transfer. The nuclei of many of the cells tended to resemble that commonly described for the large lymphoblast (Fig. 23). In some the cytoplasm was undifferentiated, but in most it was of histiocytic structure and a fair number of cells were phagocytic.

From the eighth transfer on bizarre forms became increasingly numerous and there seemed to be a general increase in cell size accompanied, however, by extreme anisocytosis (Fig. 24).

A true leukemic blood picture was seen at the sixth transfer, and there still seemed to be a greater tendency for malignant cells to enter the peripheral circulation than was the case during the middle period of H.R.1.

**DISCUSSION**

The term "reticuloendothelial system" was first coined by Aschoff to denote the system of fixed phagocytic cells. If this conception is retained the histiocyte becomes the reticuloendothelial cell par excellence, and the name of reticuloendothelioma becomes perfectly suitable for the growths described here. However, most modern workers regard this system as the origin of the blood cells, plasma cells, and histiocytes, and therefore postulate a primitive reticulum cell of wide developmental potencies. In this case it seems preferable to define proliferative lesions of this system by the dominant cell series where one can, or else to use a term such as reticulosarcoma, which indicates the system involved without commitment to any theory concerning it.

The morphology of the reticular stem cell is uncertain. In some writings it is apparently the same as the histiocyte, whilst others follow the teaching of Maximov (12), who postulated two cellular types attached to the reticular syncytium: a small multipotent cell, and fixed histiocytes. The ordinary blood cells are apparently desquamated from the syncytium in a primitive state as the recognized blast cells. The evi-
dence obtained from a study of the tumors H.R.1 and H.R.2 gives evidence that the same can occur with the histiocytes. The first has reverted fairly completely to a primitive cell, whilst the second went far towards it. This hypothesis has been further reinforced by a study of impression smears of human lymphadenopathies. The easiest to interpret are those obtained from certain patients with chronic erythroderma or exfoliative dermatitis. Inspection of sections make it clear that the great bulk of cells are histiocytic. In smears one can see numerous large primitive cells together with transitions between these and mature histiocytes. It seems logical to refer to the former as histioblasts.

The present writer is unconvinced by the accepted morphological criteria for distinguishing primitive cells as individuals. Histioblasts look very like lymphoblasts, but are usually larger.

If we accept Maximov's conception of the two types of reticular cell reticuloendothelioses might be of two kinds. In one the stem cell might proliferate without differentiation, whereas in the other there would be some tendency towards the formation of certain of the definitive forms. There is no certain record of either of these types. Of the connective tissue tumors occurring in the human liver we have the simple cavernous hemangioma and the rare hemangioendotheliohoma, and sarcomatoses types (2, 8). The second of these are vasculoformative and hemopoietic, sometimes producing histiocytes (Jaffé). The last are often spindle-celled, but some are certainly histiocytic and form the nearest approach to the murine growths. Pullinger (15) considers it possible that Hodgkin's disease is a reticuloendotheliosis, the causative agent acting directly on Maximov's stem cell and stimulating it to form the various cellular types found. This may be so, but elsewhere the present writer has given reasons for believing that the bulk of the swollen "reticular" cells are histiocytes in varying stages of differentiation (7) (Figs. 17-24).

There seem good reasons for exercising great caution in the use of the term reticuloendotheliosis, but it is far less easy to decide between the merits of histiocyto-

SUMMARY AND CONCLUSIONS

1. Histiocytomas of the liver have been principally studied in the C57 black strain of mice. They occur spontaneously in mice upwards of 18 months old, but may occur considerably earlier in those treated with carcinogenic hydrocarbons.

2. The growths are apparently of multicentric origin, arising in the sinusoids. Extramedullary myelopoiesis, which may accompany them, is generally perivascular in origin.

3. A description of nonmalignant histiocytes is given. Forms intermediate between histiocytes and monocytes may be found, whilst the nuclear structure may often resemble that of a lymphocyte.

4. Impression smears of the liver show that the dominant cell is a functionally mature histiocyte.

5. The heart's blood generally contains large numbers of malignant histiocytes.

6. Blood from the tail gives a variable picture; a few malignant cells probably occur in all late cases, but a true leukemic blood picture is exceptional.

7. Histiocytomas may have the morphology of a spindle cell sarcoma, particularly in metastases or on transplantation.

8. Two cases (H.R.1 and H.R.2) have been transplanted. In the earlier transfers both showed a definite tropism for the liver.

A spontaneous growth of identical histological appearance was found arising in the lower ileum of a mouse of the same strain whilst the author was at the Lister Institute. Unfortunately it was not transplanted.
9. Both have undergone fluctuations in virulence.
10. Once the tropism for the liver was lost they produced a malignant plastic peritonitis with metastases. The peritoneal deposits were spindle-celled. Giant cells occurred occasionally in H.R.1, but more abundantly in H.R.2.
11. H.R.1 now has the characteristics of an acute leukemia. The dominant cell is small and primitive, resembling a lymphoblast. It has retained some power of differentiation.
12. During its period of most rapid growth the cells of H.R.2 showed certain primitive features, particularly in nuclear structure. On one occasion during this period the tail blood showed the picture of a monocytic leukemia.
13. The question of the terminology of neoplasms of reticuloendothelial origin is discussed.
14. It is concluded that the histiocyte is derived from the primitive reticular cell of Maximov through an intermediary histioblast.

ACKNOWLEDGMENTS
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P. A. Gorer

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