discoloration, similar infiltrative changes, proliferation of the same cell type (astrocytes) although this proliferation is diffuse so that no neoplasm results. In some cases of multiple gliomatosis there has been a tendency for accompanying encephalitic foci to be more diffuse or to be associated with areas of diffuse gliosis confined to certain regions of the brain (see fig. 56, 57). Very large quantities of pigment were present in such a case (see fig. 84). Such cases provide lesions transitional between disseminated focal and diffuse encephalitis. Lastly, a parasitic agent has been detected in the affected areas similar to the agent to be described in focal encephalitis, cerebral abscess, and glioma of fowls. Attention the unusual pathology in this particular individual. It should be added that recognised factors causing encephalitides of birds, whether deficiencies or virus infections, could apparently be excluded.
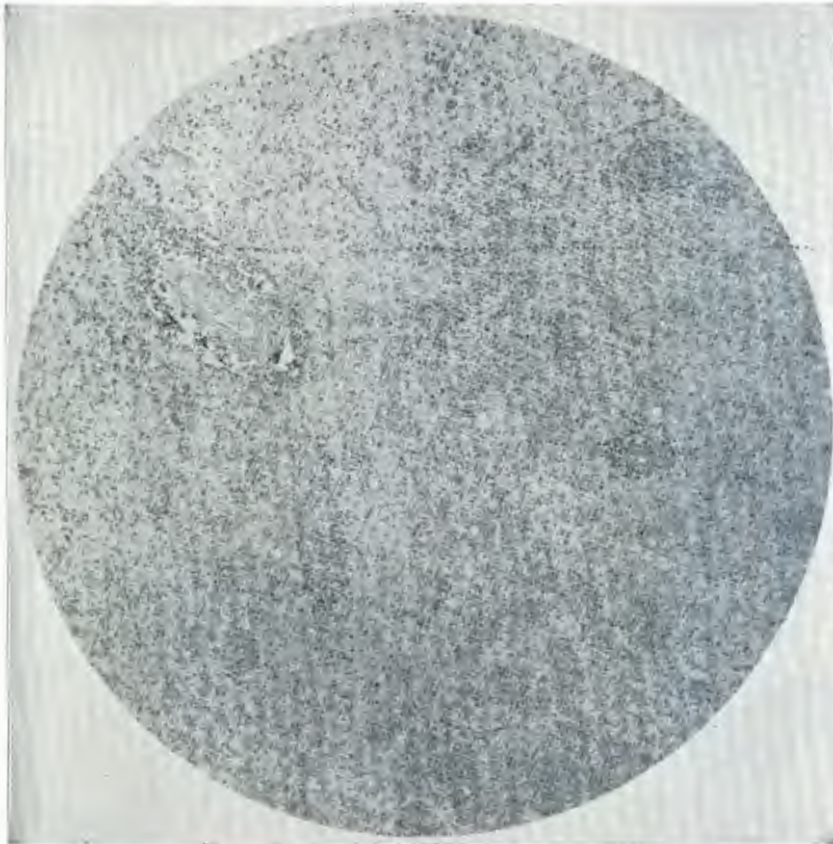

FIG. 49.—More severe grade of disseminated focal encephalitis associated with a certain degree of softening of the brain and with some participation of granular leucocytes—a lesion transitional between Figs. 48 and 51. (H.E.) X 80. (34605.)

4. *Lymphoid Tumours of the C.N.S.*

It has been mentioned that perivascular infiltration of " round cells " (fig 28), even in glioma may be pronounced; and as will be seen later it may lead to what are virtually small lymphomas in the stroma and at the reactive margin of gliomas (fig. 72).

Similarly, there are cases of non-purulent disseminated focal encephalitis, without glioma formation, in which proliferation of this cell type dominates the picture (fig. 58). The vascular and intravascular changes in such cases are similar to the more typical cases described, but perivascularly the infiltration and multiplication of lymphocytes and plasma cells is exaggerated. Histopathologically, all intergrades (fig. 59) can be traced to frank lymphosarcomas (fig. 60) or malignant plasmacytomas (fig. 61).
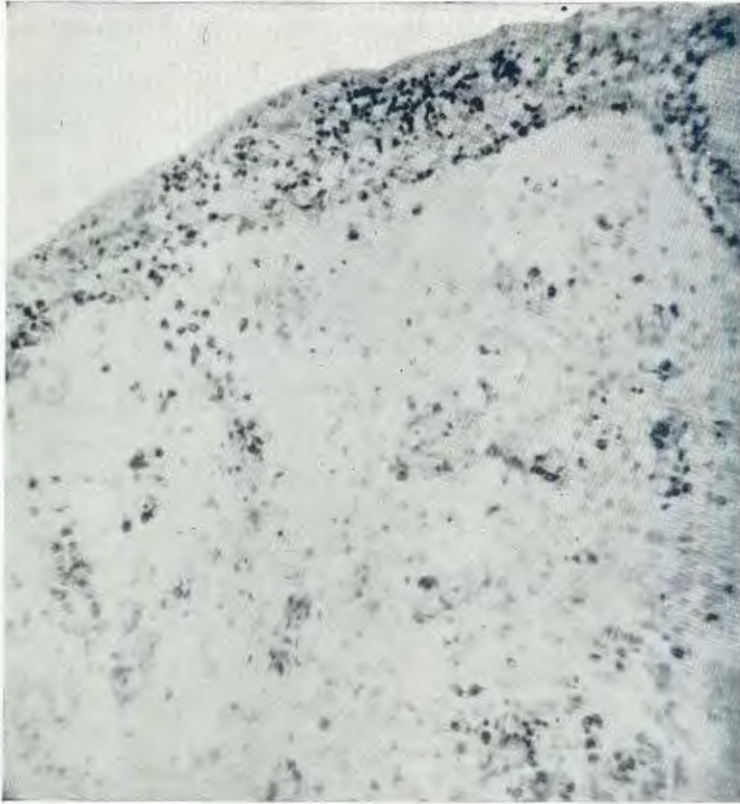

FIG. 50.—Disseminated perivascular meningo-encephalitis. Plasma cell infiltration is prominent. (Giemsa.) X 240. (34534.)

The study of these intergrades has convinced me that a very strong suspicion should be entertained that, just as gliomas are to be regarded as encephalitic foci in which progressive changes involving the astrocytes have come to dominate the picture, so these lymphosarcomatous brain tumours arise as similar encephalitic (or probably more often as meningo-encephalitic) foci in which the proliferation of lymphocytes or plasma cells gets "out of hand", and proceeds to actual invasion of the brain substance with all the classical signs of frank malignancy. In the present series of cases, lymphocytic neoplasms appear to have a predilection for the brain stem (medulla), which it will be remembered is extremely rarely the site of gliomas; the Gasserian ganglion also appears to be a seat of predilection (fig. 62). Our cases of lymphoid tumours affecting the Gasserian ganglion have

also involved the neighbouring parts of the brain—e.g. the medulla, as well as the cerebellum and optic lobe. The brain appears to become invaded from foci in the leptomeninx which may indeed have been the primary site whence both the sensory root of the Vth nerve (in an outward direction) and the underlying brain substance (in an inward direction) have been involved through spread by direct continuity. In one case of a tumour (suspected of being a glioma) attached to the surface of the optic lobe, microscopically the neoplasm was seen to be a lymphocytoma apparently having its inception in the leptomeninx, but with invasion of the adjacent brain tissue (see fig. 63). In such a case one suspects that the tumour arose in a focus of perivascular meningitis (see above).
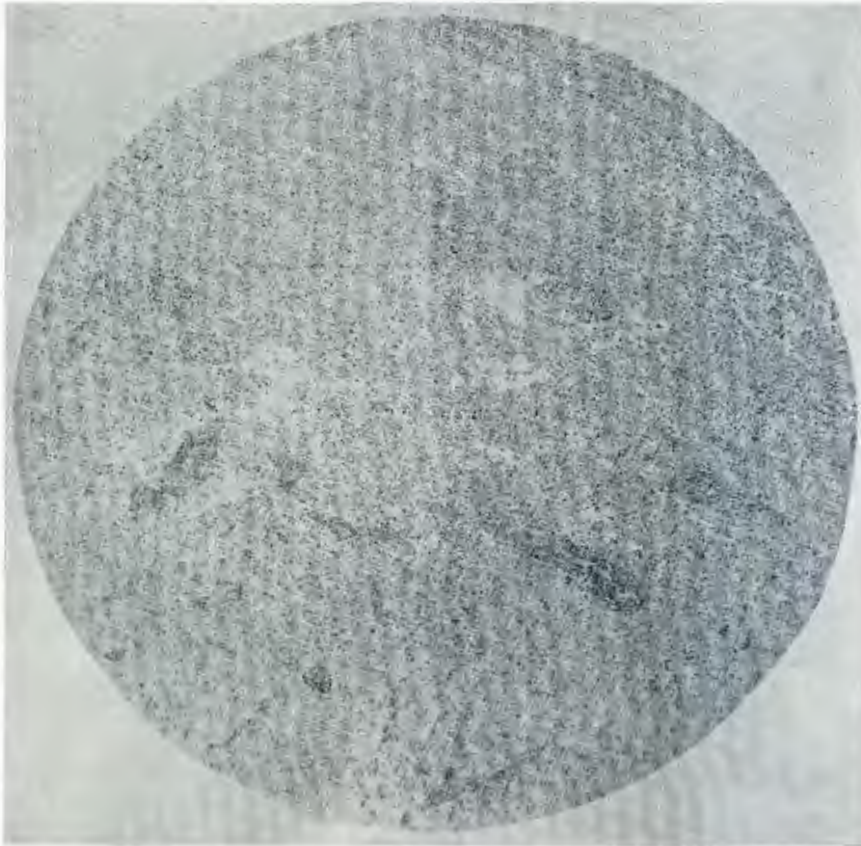

Fig. 51.—Purulent encephalitis: Multiple foci of perivascular encephalitis associated with softening and infiltration with granular leucocytes. (H.E.) X 85. (34534.)

5. *Haemangioblastoma of the C.N.S.* (*Haemangio-endothelioma*).

Although haemangio-endotheliomatosis of fowls has been extensively studied at Onderstepoort both before and since it was described by Furth (1934), these cases have concerned tumours of the skin and thoracico-abdominal organs, often multiple, from which characteristically bleeding occurs and ultimately is the

cause of death. Only two cases have been encountered where the C.N.S. was affected. Both are very instructive of different aspects of the pathology of these tumours and since no such cases occur in the literature they will be described in some detail.

Case 38158.

A White Leghorn pullet, two months old, showed an extensive subcutaneous swelling in the right fronto-parietal region. It was unable to walk, lay on its side, and was killed. At post mortem the subcutaneous mass measured ca. 3 cm. in diameter and consisted in part of a haematoma and in part of haemorrhagic tumour tissue. This tissue extended deeply through a 4 mm. defect in the skull to become continuous with a tumour mass 3·5 mm. in diameter whose deep surface was embedded in the lateral aspect of the right cerebral hemisphere. This hemisphere is greatly enlarged to at least one-and-a-half times its normal size and is orange discoloured. The left hemisphere is reduced to about half its normal size (pressure atrophy).
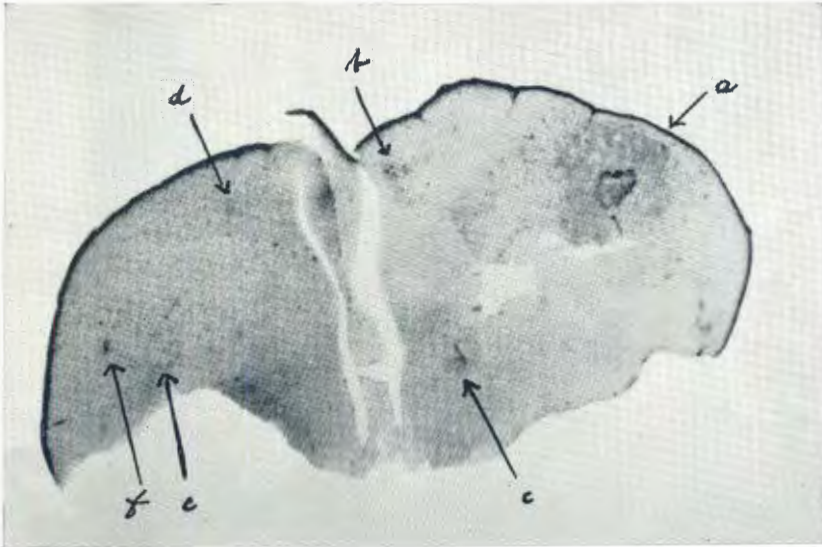

FIG. 52.—Cerebral abscess (*a*), with co-existing foci of disseminated encephalitis [(*b*), (*c*), (*d*), (*e*) and (*f*)] in the same and in the opposite cerebral hemisphere. X 6. (36684.)

Microscopically, the cerebral tumour is composed of endothelial cells backed by reticulum and collagen fibres and organised into capillary to slightly cavernous blood-spaces. There are many mitoses. The entire right hemisphere is affected by multiple disseminated encephalitis and these changes centre in and around the bloodvessels, which are increased in prominence due to connective tissue thickening of their walls and endothelial hypertrophy. The perivascular astrocytes have enlarged and multiplied, and this astrocytosis tends to be confluent, and in parts, especially near the margin of the tumour, almost diffuse. There is slight infiltration of lymphocytes, plasma cells, and cells of the monocytic series. There is tremendous perivascular and perineuronal oedema, culminating in a considerable fluid-filled but in parts also haemorrhagic pseudo-cystic space

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around the margin of the tumour. Haemofuscin pigment is demonstrable in small amount, chiefly in the hypertrophied astrocytes. Other sections show that as the tumour is followed outwards, penetrating the bone and expanding under the scalp, it tends to become increasingly cavernous to cystic and haemorrhagic.

Fig. 53.—For explanation see Fig. 54.

Diagnosis.

Haemangioblastoma of right cerebral hemisphere with penetration of meninges and skull and growth in the subcutis, occurring in association with severe disseminated focal encephalitis; the enlargement due chiefly to the latter has caused severe pressure atrophy of the left cerebral hemisphere.

FIGS. 53 AND 54.—Structure of a small (Fig. 53) and a large (Fig. 54) cerebral abscess in the fowl. Below, the purulent cavity; centre, the abscess "wall"—a zone of purulent encephalitis; above, the surrounding brain tissue showing perivascular encephalitis. (Giemsa.) X 120. . (36684 and 29351.)

Remarks.

(1) The expansion which certain primarily intracranial tumours are liable to undergo when once they have penetrated through the skull and been released from the restraining effects of intracranial pressure seems to be poorly appreciated in veterinary pathology. (The severity of pressure in the above case is attested by the remarkable degree of pressure atrophy of the unaffected cerebral hemisphere.) This phenomenon, whereby the intracranial part of a neoplasm becomes greatly overshadowed in bulk by its extra-cranial expansion, usually encourages the erroneous assessment at post mortem that such a tumour was primarily extra-cranial and penetrated the skull in an inward direction, instead of the correct interpretation, viz. the exact opposite.
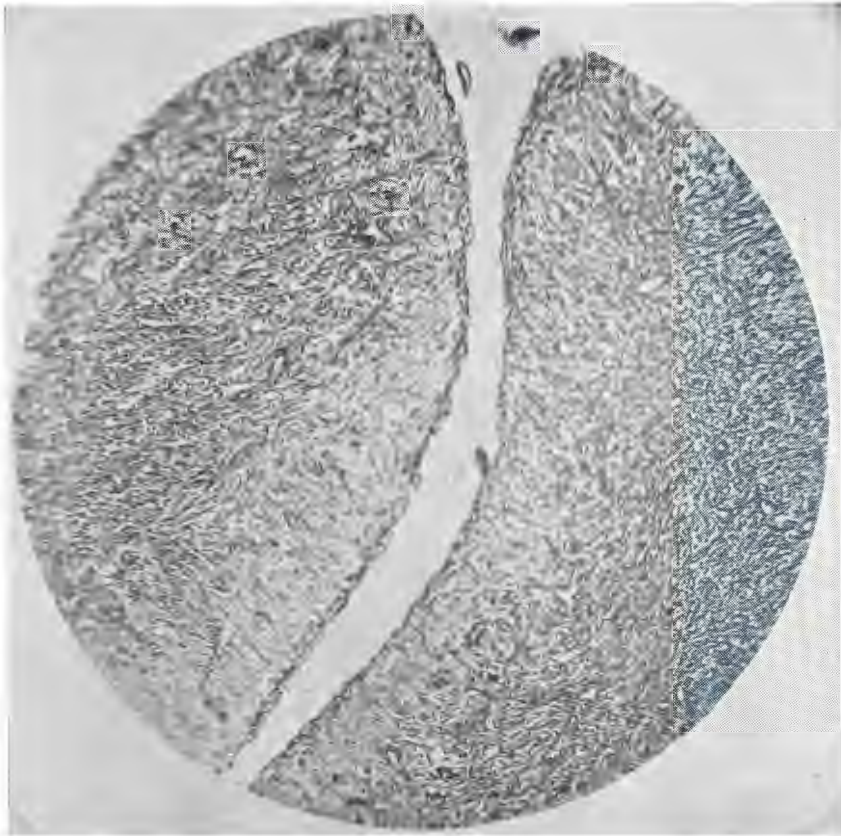

Fig. 55.—Diffuse encephalitis (diffuse interstitial gliosis) of the cerebellum. An area has been chosen where the changes do not reach maximum severity and where all microscopic landmarks become obscured. Two adjacent cerebellar foliae of which the molecular layer is still recognisable in the one on the left, but in the one on the right is only recognisable with difficulty below. Elsewhere this layer is a highly cellular tissue composed of proliferating glia cells. The Purkinje cells have been obliterated. In the granular layer, granule cells are still seen in fair numbers among the proliferating glia elements in the case of the left folia, but in the right one they too have been virtually obliterated. (Phosphotungstic acid haematoxilin.) X 135. (32375.)
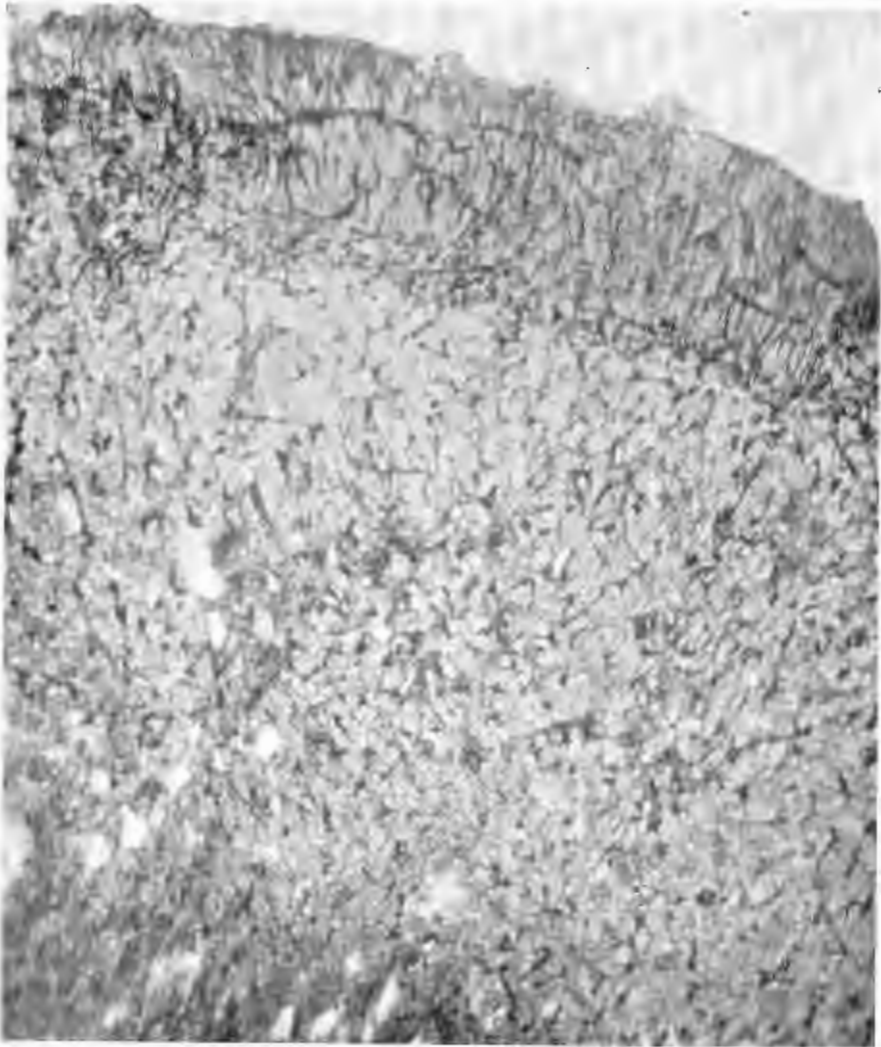
FIG. 56.—Lesions transitional between focal and diffuse encephalitis in the cerebellum, affecting chiefly the molecular (above) and the granular layer (below). (Cajal's gold sublimate.) X 160. (35299.) Multiple type II gliomas were present, the cerebrum, optic lobes and cerebellum (centrally) being affected.

FIG. 57.—High power view of the lesions shown in Fig. 56. Tendency for the astrocytosis to be diffuse, although largely perivascular. (Cajal's gold sublimate.) X 350. (35299.)
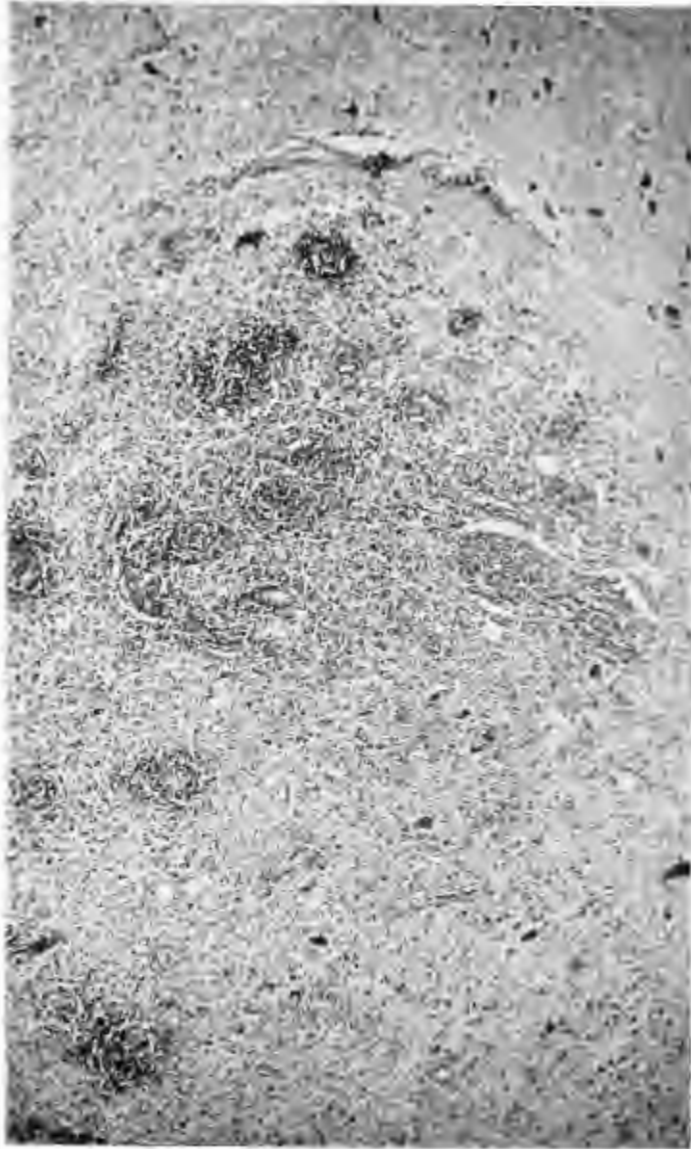
FIG. 58.—Disseminated focal perivascular encephalitis with exaggerated proliferation of lymphocytes—a lesion transitional between encephalitis and lymphocytoma. (The neighbouring leptomeninx was involved also.) (Giemsa.) X 120. (35912.)

(2) As in the second case (reported below), the association of haemangio-blastoma with astrocytic proliferation approaching astrocytomatous grade and (in the above case) also with cyst-like cavity formation in the brain around the tumour should be compared with Lindau's disease (of man) in which haemangio-blastoma is present as a mural nodule in an astrocytomatoid (if not actually astrocytomatous) cyst.

(3) The association of haemangioblastoma with disseminated encephalitis of vascular and perivascular distribution (causing great enlargement of the affected hemisphere) and characterised by discoloration due to " haemofuscin " pigmentation will be encountered again in the second case (below), when it will be further commented upon.
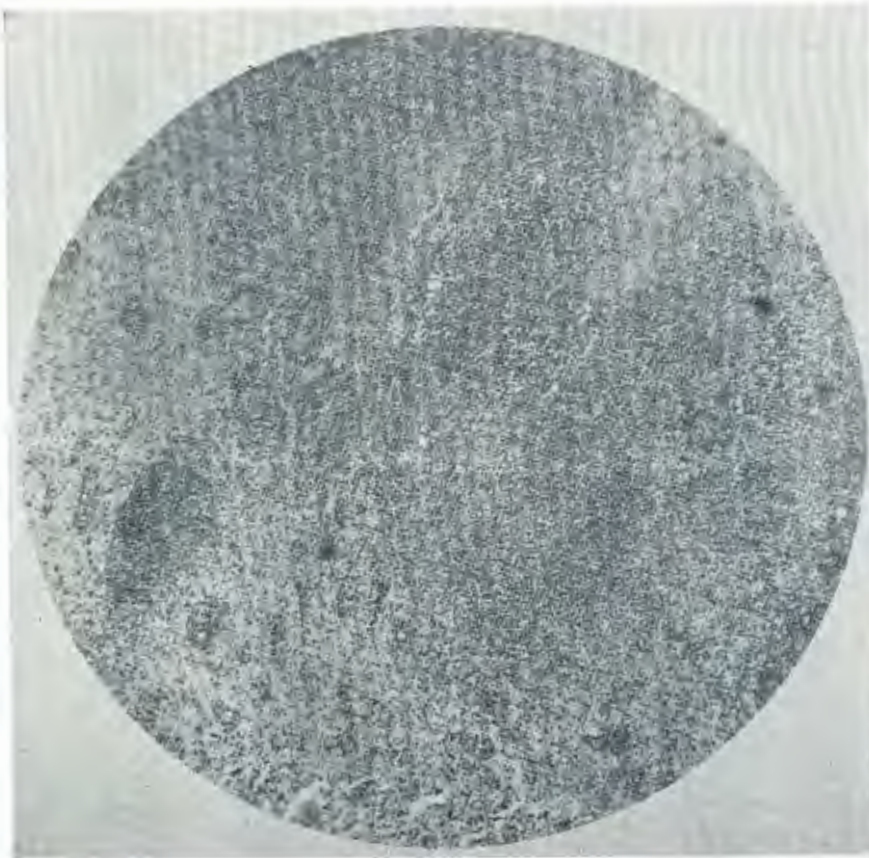

FIG. 59.—Actual transition between perivascular focal encephalitis (with exaggerated lymphoid hyperplasia) (left) and plasmacytomatous tissue (right). Cerebral peduncle. (Giemsa.) X 120. (34536.)

Case 36755.

Both cerebral hemispheres of a W.L. pullet aged 4 months were much enlarged and orange discoloured. In addition there were three dark blue circumscribed foci (suspected haematomata), one on the surface of the right

hemisphere, one in the substance of the left hemisphere but situated near enough to the surface to be readily visible externally, and another deep in the substance of the left hemisphere. These foci varied from 2 to 0·5 mm. The rest of the post mortem was completely negative.

Microscopically the findings were disseminated perivascular encephalitis characterised by very limited exudation of leucocytes, heavy " haemofuscin " pigmentation of the vessel walls, and marked reactive gliosis, in parts tending to become diffuse and approaching astrocytomatous grade. The leptomeningeal
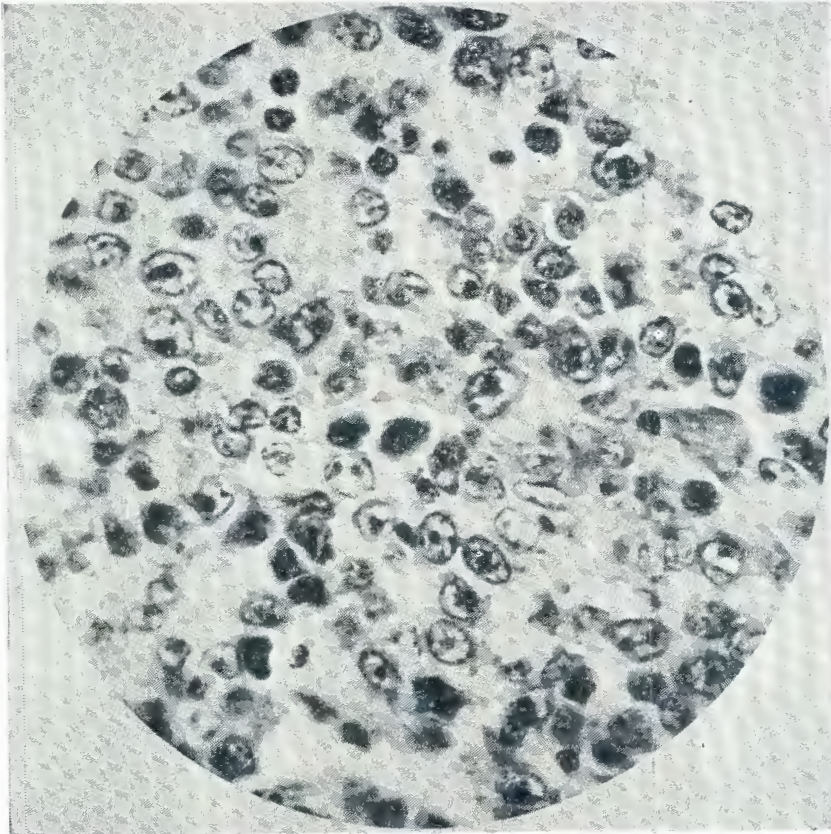

FIG. 60.—Frank lymphocytoma of medulla oblongata. The majority of the cells are lymphoblasts and lymphocytes, with a minority of lymphocytic plasma cells (cf Fig. 61). Numerous mitoses. (H.E.) (34535.)

vessels are similarly affected. The foci mentioned above were capillary haemangio-endotheliomas—one of the leptomeninx and two of the cerebrum; and the larger they are the more distinct tendency they show to become cavernous. The larger ones are surrounded by haemorrhages i.e. they form roughly the centre of the small haematomata described (fig. 64). In addition, few but multiple tumours of dimensions of 0·15 to 0·25 mm. were disclosed in the cerebrum only on

microscopic examination. These proved to be solid haemangioblastomas (figs. 65, 66, and 67) and in some cases they could readily be traced into continuity with the endothelium of pre-existing small bloodvessels. The larger ones already show a tendency to become capillary and later cavernous (figs. 67 and 68).

Even in this earliest stage, " haemofuscin " pigment particles can be demonstrated in the neoplastic endothelial cells (see fig. 65). This is before blood starts to circulate through the tumour tissue and of course long before any haemorrhage occurs (at which stage this observation might lose its significance).
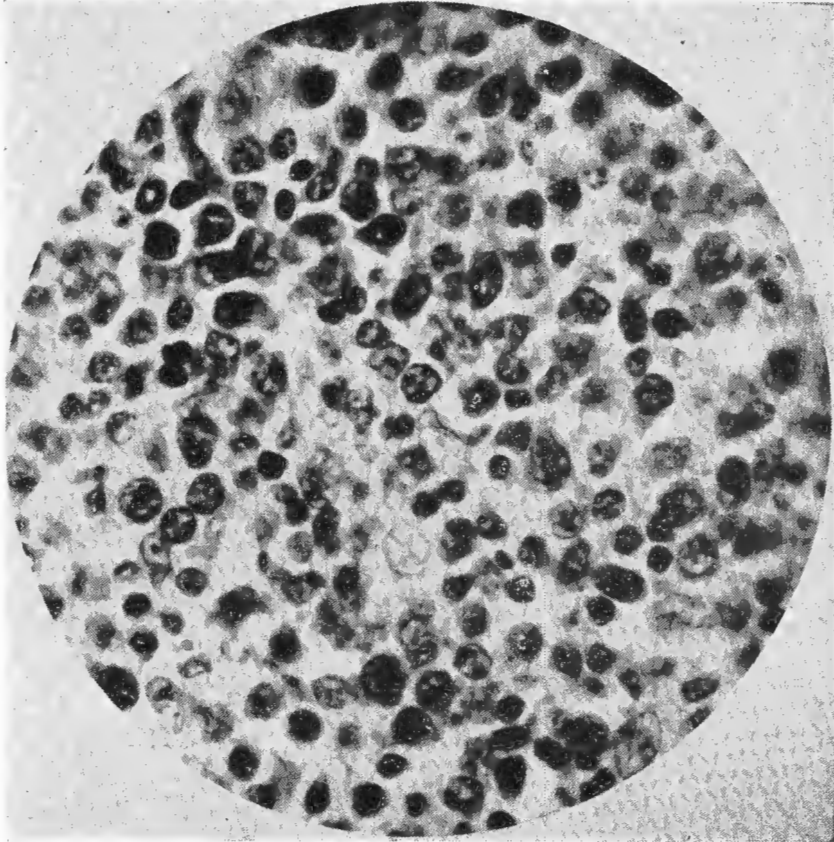

FIG. 61.—Plasmacytoma of cerebral peduncle. The majority of the cells here are plasma cells (both lymphocytic and lymphoblastic) (cf. Fig. 60). Numerous mitoses. (H.E.) X 1500. (34536.)

Around one of the larger haemorrhagic haemangioblastomas described, a much more pronounced degree of astrocytic proliferation than that shown in fig. 64 was seen. This area of altered cerebral tissue shown in fig. 69 would, if encountered alone, doubtless be diagnosed as astrocytoma—a tumour which, as was mentioned earlier, has not been encountered in the fowl.

Remarks.

(1) In this case again the tumours occur in a brain affected by encephalitic lesions centring in and around the bloodvessels. Unlike the previous case, both cerebral hemispheres are affected by encephalitis, and it is significant that here the tumours also develop in both hemispheres. Again this encephalitis is characterised by "haemofuscin" pigmentation.

(2) The earlier stage of development of the tumours in this case enables one to produce still more precise evidence to support the above-mentioned indications that they are significantly related to the encephalitis; for—as in the case of the gliomas—one is able to follow the neoplasms back to their inception, when they are seen to merge into and indeed to arise as foci of encephalitis centring around and especially in the bloodvessels.
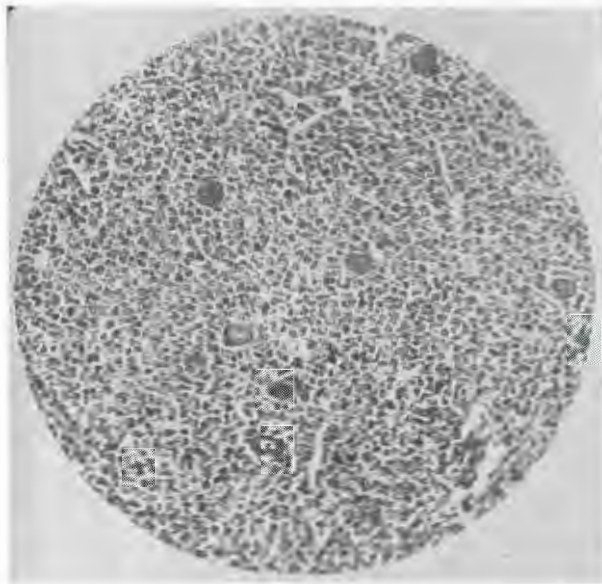

FIG. 62.—Lymphocytoma of the Gasserian ganglion. Note surviving ganglion cells. (H.E.) X 125. (35636.) See also Fig. 85.

(3) The study of this case shows clearly that solid, capillary, cavernous and cystic haemangioblastomas are but stages in the life history of an endothelial neoplasm. At the inception of such a tumour there is proliferation of endothelial cells in solid formation; later—and parallel with the development of reticular fibrils by these cells—there is organisation of capillary lumina; these in turn become distended by circulating blood into wider spaces. As in the case of multiple gliomas, the multiplicity of these haemangioblastomas of the brain is to be regarded as primary, each tumour having origin independently from an encephalitic focus in which vascular changes from the outset predominated over pervascular changes. [8] The earliest minute lesions, in which even reticular

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([8]) However it would not be appropriate to comment here on the equally interesting question of primary multiplicity *versus* metastasis in the ordinary cases of haemangio-endotheliomatosis of fowls affecting skin and (or) abdominal organs.

fibres are poorly developed, would present a nice histopathological puzzle in differential diagnosis, were it not for the gradation seen to tumours which declare their nature on account of a higher degree of organisational pattern which emerges in the later history of these neoplasms.

(4) In this case also the astrocytomatoid proliferation is most pronounced around the neoplasms. Attention has already been directed to the significance of this for the understanding of the pathogenesis of the lesion found in Lindau's disease. The absence of cyst-formation in our second case may well be due merely to the much younger age of the lesions.

FIG. 63.—Invasion of the brain by lymphocytoma arising in the leptomeninges. A focus of perivascular leptomeningitis (top right) in which (top centre) lymphoid proliferation becomes exaggerated to form an actual small lymphocytoma (top left). This then invades the subjacent brain tissue (left of centre). Compare Fig. 50. (Giemsa). X 120. (29338.)

As in the case of gliomas (and intracranial lymphosarcomatous tumours), so also one finds evidence (although perforce based on the study of far more limited material) that intracranial haemangioblastomas can be traced pathogenetically as variants of the neoplastic processes which arise in encephalitic foci characterised
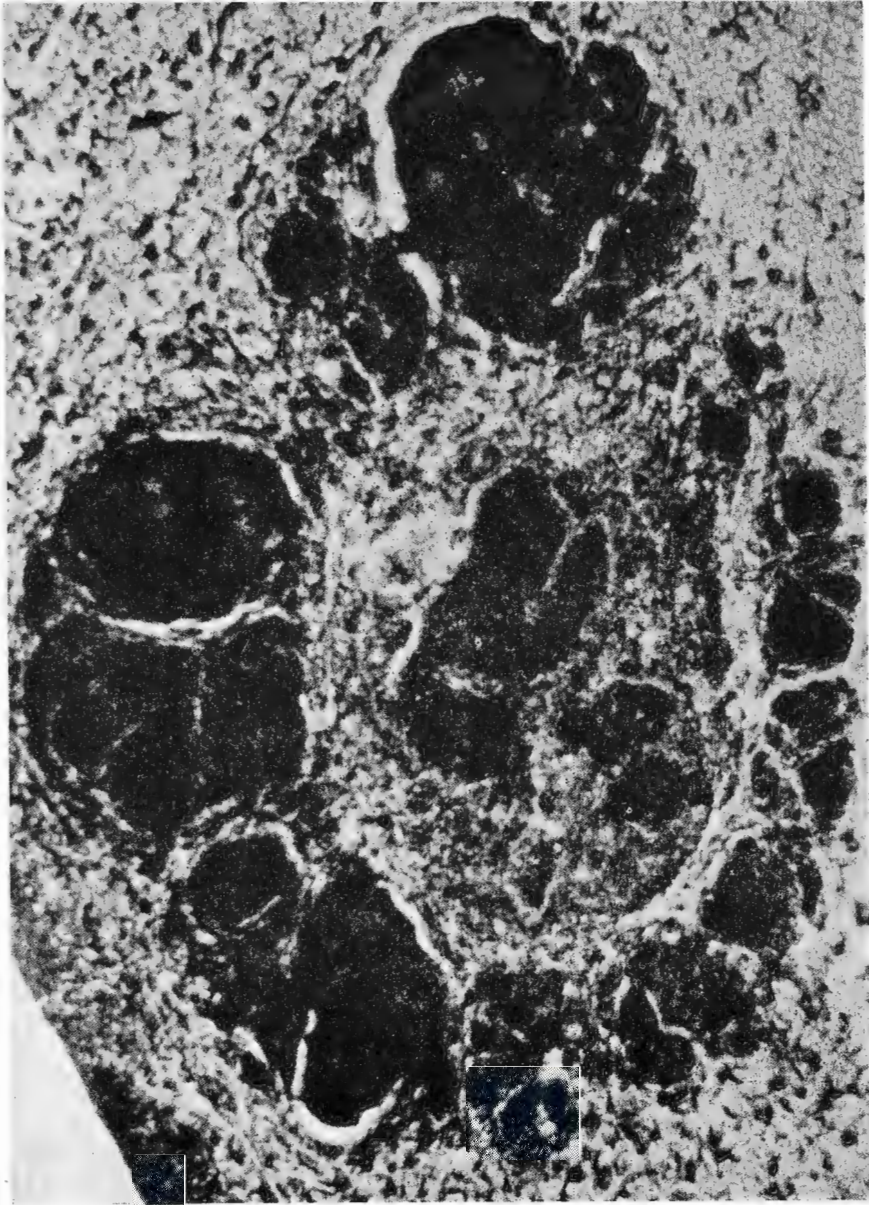
FIG. 64.—Haemangioblastoma of cerebrum. Centre—capillary to cavernous structure of the tumour, from which blood escapes to form multible haematomata around its periphery. Marginal astrocytosis. (Cajal's gold sublimate.) X 150. (36755.)

by "haemofuscin" pigmentation. All that is necessary to observe the crucial evidence for this hypothesis is the opportunity to encounter the earliest stages of such neoplasms, i.e. tumours which are still of microscopical dimensions, although even in more advanced cases the extraordinarily regular association of neoplasia with encephalitis is a signpost clearly pointing in this direction.

FIGS. 65-68.—Stages in the development of the lesions of a case of multiple cerebral haemangioblastomatosis. (36755.) See also Fig. 64.
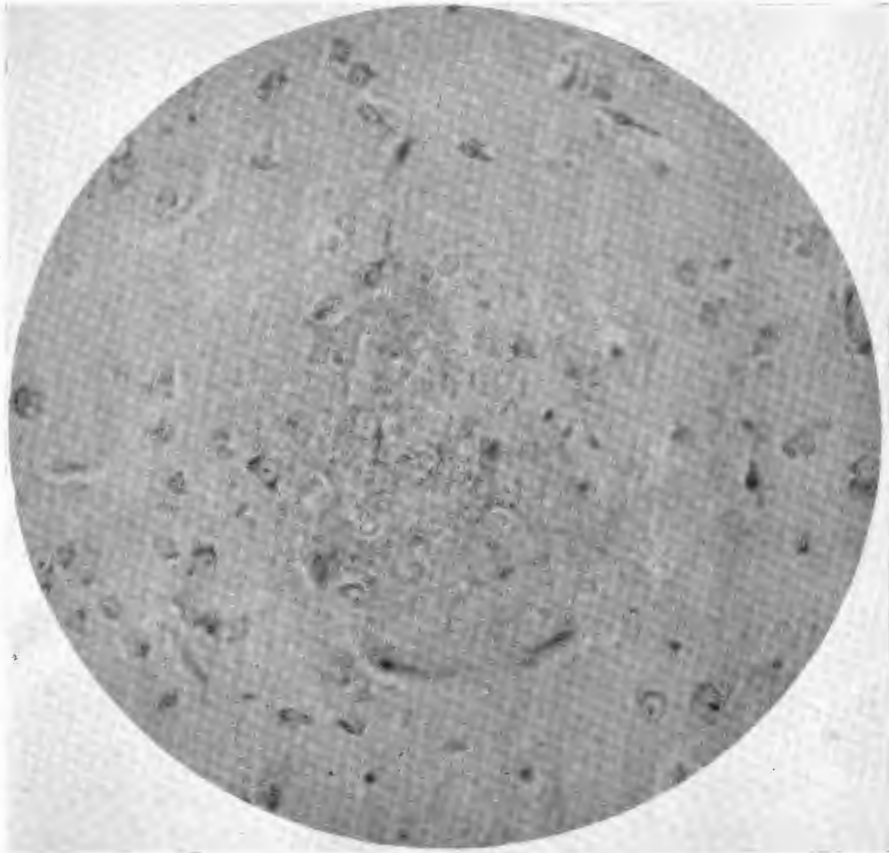

FIG. 65.—Earliest recognisable lesion in multiple haemangioblastomatosis of cerebrum. A minute focus (of encephalitis) in which from the start endothelial proliferation predominates. The endothelial cells are in patternless arrangement and virtually no reticulum fibres have been produced at this stage, which could probably be interpreted only by following backwards from the more advanced lesions shown in the succeeding figs. Fine darkly staining granules of "haemofuscin" pigment can be seen. (Giemsa.) X 150.

6. *Mixed Gliomatous and Mesenchymal Tumours.*

Under this category may be grouped certain cases in which brain tumours contain, in addition to the glial moiety as previously described, proliferations of haematogenous cells on a scale which, according to the orthodox criteria of

pathology, may be adjudged "to have reached neoplastic grade". The considera-
tion of these neoplasms was postponed until the origin and nature of the infil-
trating cells in simple gliomas should have been described. As was seen, such
cells—a relic as it were of the encephalitic origin and spread of gliomas—have
emigrated from the blood and possess proliferative ability. In the two tumour
variants to be described here, they form a coherent tissue and sometimes indeed
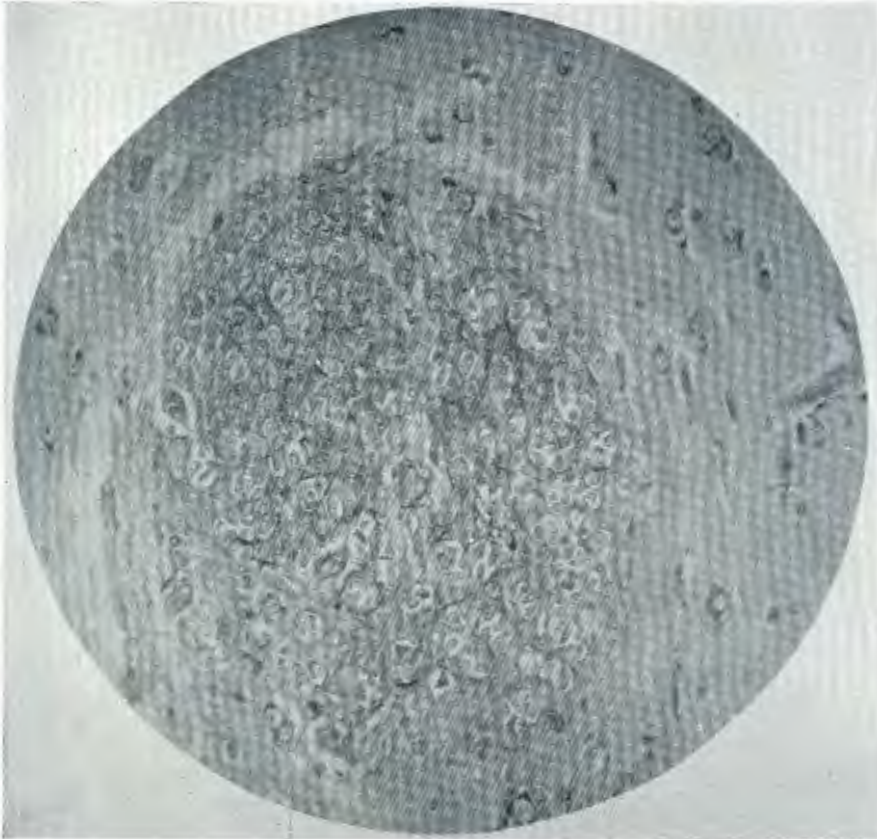overshadow the glial moiety.

FIG. 66.—Further stage in the development of haemangioblastoma. The endothelial cells
have grouped themselves into solid units which will later develop capillary lumina and
are commencing to lay down connective tissue fibres. (A minute solid haemangio-
blastoma.) (Giemsa.) X 450.

(1) *Type II (a).—Glioma lymphomatosum.*

Perivascular lymphocytic infiltration and multiplication at the margin of
gliomas has already been mentioned. It may become pronounced while still
falling under the category of mere lymphoid hyperplasia. It has also been
explained how such vessels with their surrounding mantles of lymphoid cells
become incorporated as a stroma between the lobules of glioma. However,
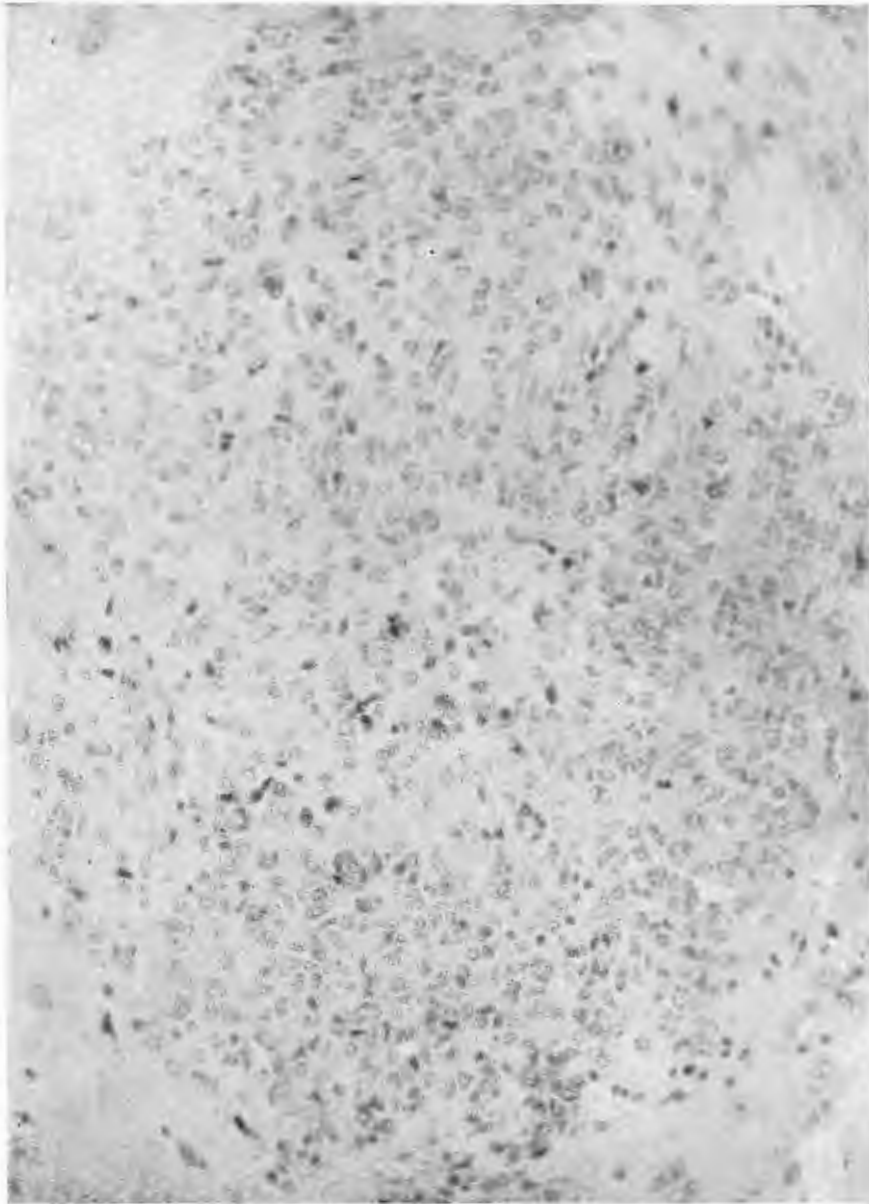fig. 70 illustrates a case in which this phenomenon has reached a still higher

FIG. 67.—At this stage of development of haemangioblastoma, the first traces of circulation through capillary lumina can be seen: In a still chiefly solid tumour, erythrocytes (darkly stained) are seen here and there within capillary lumina. (Transition from solid to capillary haemangioblastoma. A reactive astrocytic moiety is also seen to be present—the *large* pale nuclei.) (Van Gieson.) X 450.

FIG. 68.—Later stage in the development of haemangioblastoma. A capillary haemangioblastoma (above) is seen becoming cavernous (below). Haemorrhages into surrounding brain substance. (Giemsa.) X 150.

grade and where the lymphoid cells form an apparently autonomously prolifera-
ting tissue admixed with the gliomatous tissue. Here actual lymphoid nodules
with germ-centres (secondary nodules) are formed—a proliferation which, if
occurring alone, would be assessed as lymphomatous in nature. The glioma tissue
is of the usual type II. Only one case in this series was classified as type IIa;
but in several cases classified with ordinary type II tumours, a tendency towards
this degree of lymphoid proliferation existed (i.e. intergrades between types II
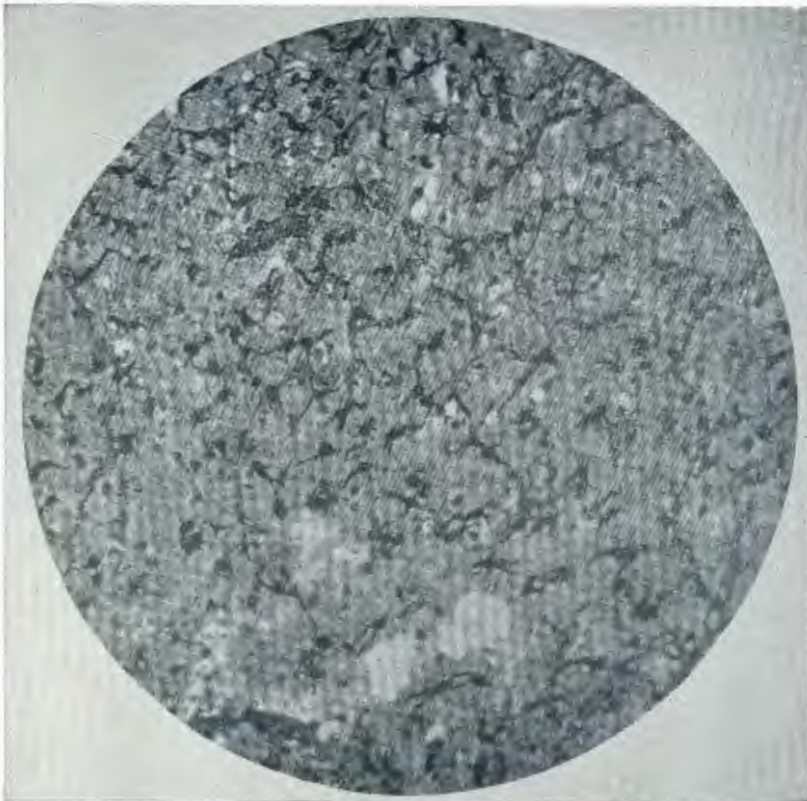and IIa occur).

FIG. 69.—Astrocytic reaction around the margin of a haemangioblastoma (below, only just
    included within the edge of the field). This reaction approaches astrocytoma grade.
    Astrocytoma has not been observed in the fowl, but if encountered out of its topo-
    graphical relationships, this lesion would doubtless be diagnosed as astrocytoma.
    (Cajal's gold sublimate.) X 150. (36755.)

(2) *Type II (b)—Glioma monoblastomatosum.*—This term was coined with some
hesitation, not on account of any doubt of its accuracy but because it sounds
somewhat clumsy. Some name is however necessary to describe these lesions,
although its exact construction may well vary according to individual taste. In
these gliomas it is the proliferation of cells of the monocytic series which appears
to have attained neoplastic grade and thus constitutes the second neoplastic
moiety. Figs. 71 and 72 show a tumour in which these elements, forming a
substantial tissue, may even predominate over the gliomatous tissue (seen chiefly

to the left in fig. 71) and multiply (by mitosis) much more rapidly than the latter, so that even the term "gliomonoblastoma" might be justified. However, these tumours do not spread or infiltrate in frankly sarcomatous fashion. These cells of the monocytic series were originally derived as haematogenous infiltrating elements in the encephalitic foci which precede the tumours. But in spite of this origin they do not later preserve a perivascular habitus, probably because they are very motile. They are characteristically arranged in small packets or columns which tend to be quite sharply demarcated from one another by the intervening processes of the glia cells. They have a pronounced tendency to differentiate into a type of plasma cell (monocytic or monoblastic plasma cell) differing from
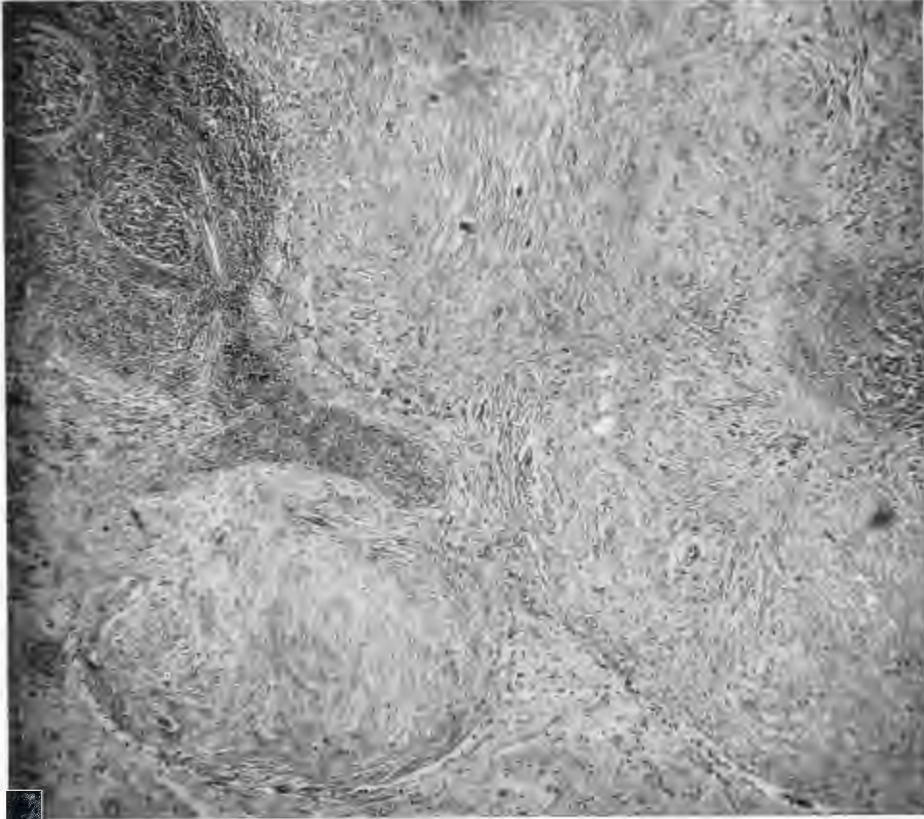

FIG. 70.—Glioma lymphomatosum. Benign lymphoid neoplasia near the margin and in the stroma of glioma, with presence of germ centres in the well-defined lymphoid nodules. (Giemsa.) X 120. (36200.)

lymphocytic plasma cells: leptochromatic—although trachychromatic—nucleus, angular cytoplasmic outline on account of accurate adaptation to the space occupied by the cell. This cell type is illustrated in fig. 2, but the appearances in the mixed tumours are best seen in fig. 73. These type II (b) gliomas are not uncommon, constituting 14·5% of the Onderstepoort cases of avian glioma. They were always multiple and in all cases gradations could be traced from encephalitic foci in which from the start emigration and proliferation of cells of the monocytic

series predominates over other haematogenous infiltrating elements. As before. the transition from microscopic foci to actual tumours is so extremely gradual that one is again impressed with the futility of striving to establish any arbitrary borderline between the inflammatory process and neoplasia.

Type II (*b*) tumours may co-exist with ordinary type II gliomas and sometimes the one type tends to predominate in one division and the other in another division of the same brain. There also occur tumours transitional between type II and type II (*b*).

The author was slow to appreciate the true nature of the mesenchymal moiety of type (*b*) gliomas, and at one time entertained the erroneous idea that he had here to deal with a proliferation of oligoglial elements.
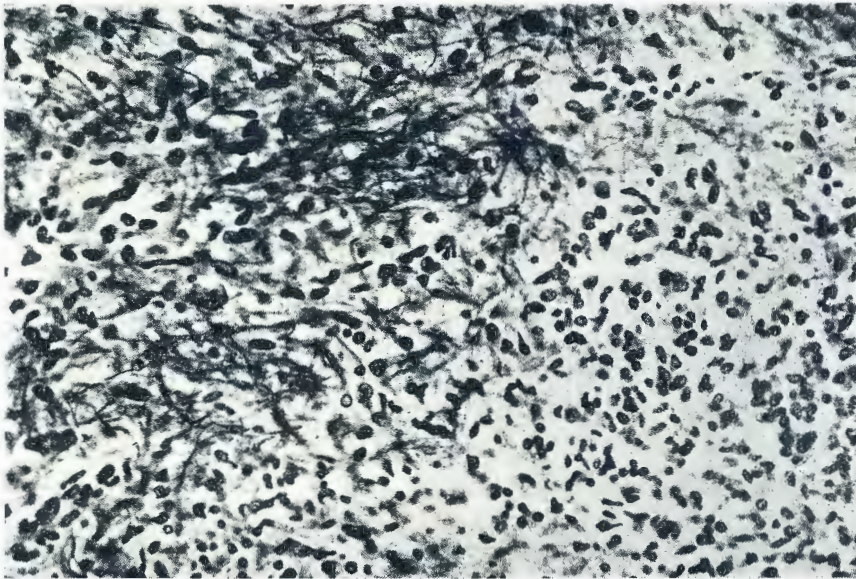

FIG. 71.—Glioma monoblastomatosum. Neoplastic glia cells are seen chiefly to the left and above, with their cytoplasm (including processes) impregnated by silver. The rest of the tumour tissue, which on the right and below prodominates to the exclusion of glia cells, is composed of monoblasts (the relatively pale oval nuclei), monoblastic plasma cells (appearing very dark) and all transitions between the two. There were concomitant liver tumours in this case. (See Figs. 77-79.) (Hortega IV.) X 400. (34607.)

Since the infiltrating haematogenous cells in avian gliomas and avian encephalitis may come to proliferate on a neoplastic grade, one might theoretically ([9]) expect to encounter such proliferations of other haematogenous elements than the two mentioned above: lymphocytic plasma cells (giving glio-plasmacytoma) and myelocytes (glio-myelocytoma). In addition one might expect

([9]) Theoretically; but in practice there might well be limiting factors, e.g. if lymphocytes proliferate in malignant fashion they may well do so so rapidly as to outgrow the gliomatous moiety. And in the case of myelocytic elements, although these are capable of proliferating by mitosis in the C.N.S., the environment may perhaps preclude proliferation on an actual neoplastic scale. So far as I know, the C.N.S. is spared in otherwise generalised avian myelocytic leukosis.
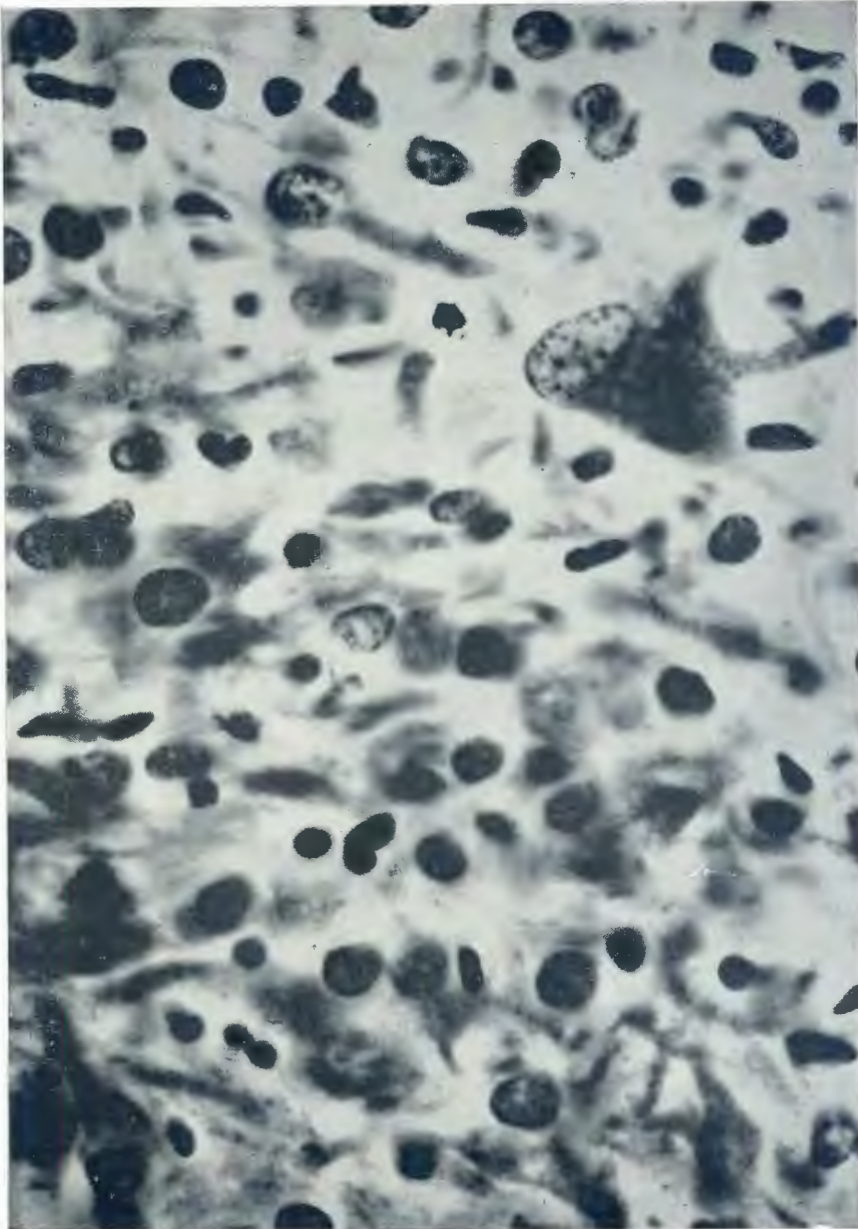
Fig. 72.—Cytology of glioma monoblastomatosum, from the same case as Fig. 71. The cytoplasm of the large glia cells including their processes is impregnated by silver. Among these elements are scattered cells of the monocytic series (with oval or kidney-shaped nuclei and cytoplasm poorly visible) and monocytic plasma cells (darkly stained). (Hortega IV.) X 1500. (34607.)

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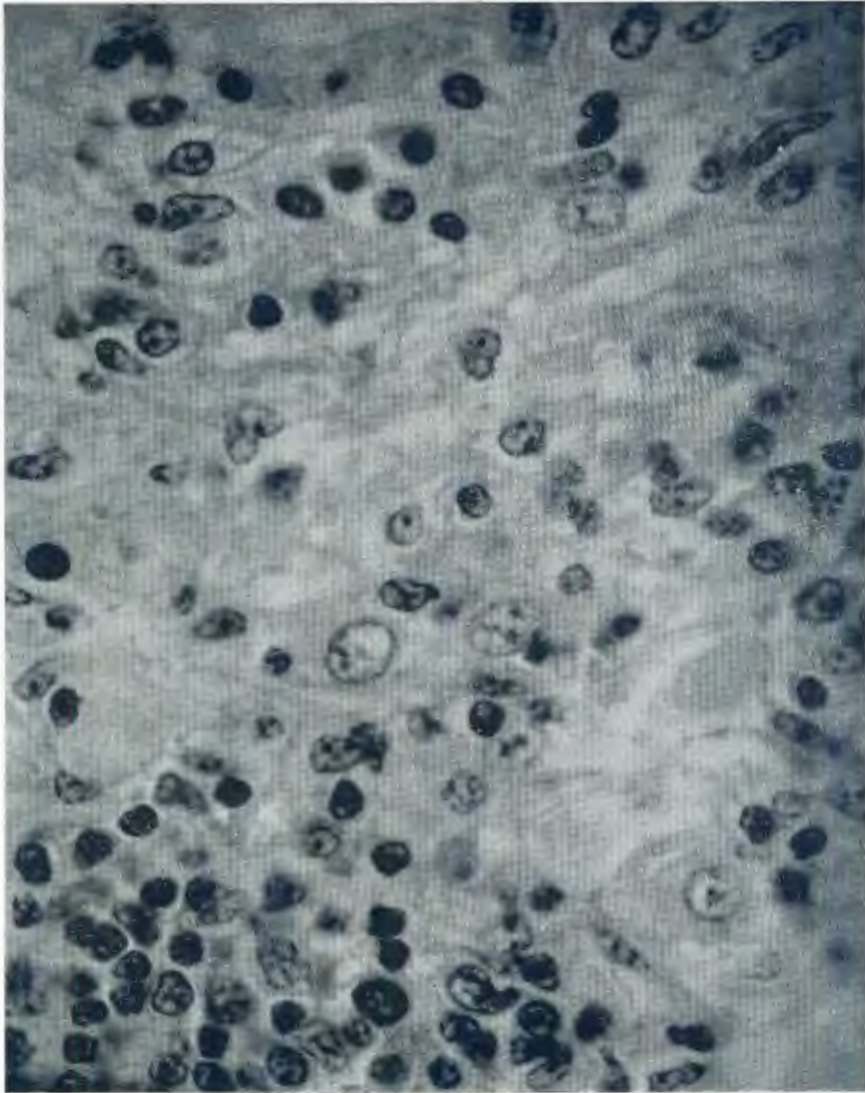Fig. 73.—Cytology of glioma monoblastomatosum (same case as Figs. 71 and 72), but with the mesenchymal moiety emphased by the technique. The glia cells (with large vesicular nuclei) are here poorly demonstrated, but the cells of the monocytic series (with smaller, also vesicular nuclei) are well seen, as well as their transitions to mono-cytic plasma cells with darkly stained cytoplasm and often with triangular or quadrilateral outlines. Mitoses are present among the cells of this moiety. (H.E.) X 1500. (34607.)