MYELOLIPOMA IN THE ADRENAL CORTEX

(MYELOADIPOSE STRUCTURES)*

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The terms heterotopic bone marrow and extramedullary hematopoiesis, often used synonymously, are associated in the physician's mind with anemia or other hematopoietic disorders. Circumscribed lesions of this nature, called myelolipomas, are seen on occasion in the adrenal cortex at necropsy. While authors of some papers dealing with these lesions record the presence of anemia, others note its absence, and even those reporting impressively large lesions pass in silence over the problem of pathogenesis. Therefore, a discussion of structures similar to bone marrow but not associated with a manifest disorder of the blood-forming systems seems indicated. A well known modern textbook of pathology says of the adrenal myelolipoma: "There may be no anemia and no other foci of extramedullary hemopoiesis,"[1] thus creating the impression that they are present in most cases.

Circumscribed bone marrow-like structures in the adrenal were first recognized by Gierke[2] in 1905, and were given the generally accepted name myelolipoma by Oberling[3] in 1929. Biressi[4] used the more comprehensive designation, myeloadipose structures. The statement that Arnold reported a myelolipoma in 1866 is based on an error in reference. The "adrenal lipomas" of Mattei (1883),[5] Brüchanow (1899)[6] and Marchetti (1904)[7] probably were myelolipomas. I have never seen a lipoma of the adrenal or read a convincing description of one.

MATERIAL

Fifty myelolipomas from the Armed Forces Institute of Pathology were studied and compared with an approximately equal number reported in the literature. In addition, the adrenal glands removed at 117 necropsies, which I performed at the Veterans Hospital, Topeka, Kansas, were studied especially for fat cells and so-called lymphocytes in the cortex. Added to these were the adrenal glands from 23 burn victims, those from 29 cases of sudden traumatic death and 29 cases of starvation, and finally more than 100 from domestic and captive wild animals.

* Received for publication, October 4, 1957.

General Observations

Grossly, most myelolipomas resemble lipomas (Fig. 1), but when myeloid tissue is abundant, the cut surfaces may be gray or red. Hyperemia and hemorrhage can alter the appearance profoundly. Various queer shapes result from the location and expansion of the lipoma-like masses (Figs. 2, 15). The myelolipoma may arise in cortical tissue, irrespective of its location, and, since cortical tissue may be present between the layers of the capsule or outside the capsule in the periadrenal fat, myelolipomas may also arise there (Figs. 4, 5). One cannot determine definitely which of the three layers of the cortex is the site of origin, because sharply localized, sufficiently small lesions are rare, but the inner half of the *zona fasciculata* seems to be the principal site of myeloadipose changes. An extracapsular myelolipoma need not have originated in an outer layer or a central one in an inner, because the three layers can be inverted in the central cortex as well as in portions of cortex which extend beyond the capsule. When a large fatty nodule reaches the capsule, leaving little or no remnant of cortex beneath it, its appearance may be puzzling, especially when periadrenal fat is abundant (see legend to Fig. 12). A myelolipoma situated between the layers of the capsule or in the periadrenal fat tissue may have arisen in any of the three zones, since cortical tissue which extends into the periadrenal fat may lose its regular layering.[8] Indeed, pigmented cells of the *zona reticularis* may be found in the outer portions of extracapsular cortical tissue.

The lesions exhibit all gradations from almost entirely adipose to almost entirely myeloid tissue (Figs. 3, 7, 8, 13, 15). The ratio of fat tissue to myeloid tissue is difficult to judge when, as I have seen in two cases, the myelolipoma is formed in cortical tissue which has grown through the capsule into the periadrenal fat (Fig. 5). It may be impossible to decide which is original periadrenal fat and which the fat tissue that developed in the extracapsular cortex as part of the myelolipoma. Small and medium sized nodules may be almost entirely fatty or entirely myeloid. The cellular marrow often is peripherally located, while the fat is central; the reverse may also occur (Figs. 8, 15).

Connective tissue plays a minor role, and no continuous fibrous layer separates the myelolipoma from the surrounding cortex; thus, it does not have a true capsule. Compression and condensation of surrounding tissue may result in pseudocapsule formation around a nodule, or unequal growth may produce apparent septation within it (Fig. 15).

The gross appearance of a circumscribed myelolipoma often does not differ from that of a lipoma, and the diagnosis "lipoma of adrenal cortex" appears in necropsy protocols and in the literature.[5-7] But large lipomas are lobated, whereas large myelolipomas are not.

In the absence of a capsule, there is no sharp dividing line between the cells of the cortex and those of the myelolipoma. The contour of the lesion is wavy (Figs. 7, 8, 13) or irregular, with fat cells extending into the surrounding tissue, and portions of cortex protruding into the myelolipoma (Figs. 7, 13). Bits of well preserved cortical tissue occasionally are surrounded on all sides by the bone marrow-like tissue (Figs. 21, 22). The surrounding cortical cells may be either unaltered or compressed, without relation to the size or cellular composition of the myelolipoma. Perhaps it does not expand steadily, and the presence or absence of compression depends upon the phase of growth at the time of death.

Some myelolipomas, notably those containing much myeloid tissue, approach a spherical shape, are sharply outlined, and compress the surrounding tissue, obviously as the result of concentric expansion. Less regular shapes and irregular outlines probably indicate pluricentric origin and growth by apposition. Evidence of both mechanisms may occasionally be seen in the same specimen. Pressure alone cannot explain the thinning of the cortex. Narrow strips of fat tissue stemming from a myelolipoma may even extend to the capsule through a thick layer of otherwise intact cortex.

Forty-three specimens could be measured. None were spectacularly large; the largest measured 4 cm.; 5 were between 2 and 4 cm.; 18 between 1 and 2 cm.; 11 between 0.5 and 1.0 cm. The remaining 9 were slightly less than 0.5 cm. in diameter. Myelolipomas may grow very large. The bilateral adrenal masses Holliday[9] observed measured 6 by 5.5 by 4.5, and 4.5 by 4.5 by 2.5 cm., respectively. The greatest diameter in the case reported by Richardson[10] and in that of de Navasquez,[11] was 8 cm. In van Dam's[12] case the myelolipoma was twice the diameter of the normal kidney. Even these unusually large tumors did not give rise to symptoms. The two almost entirely cellular myelolipomas in the material described here were of medium size. Large ones as well as small ones were wholly or almost entirely fatty.

Some reports have stated that no medulla could be seen in the sections. In one case (Barten,[13] case 2), the whole adrenal was examined in step series, but no medulla was found. Only a small area of medulla was identified in one of my cases, although more than 20 blocks were cut.

Microscopic Observations

The myelolipoma consists of fat cells and of cells that are identical with or similar to bone marrow cells, and lymphocyte-like elements, but the variations in numbers, arrangement, and ratio of the components may make it difficult to decide whether or not the diagnosis should be myelolipoma. Numerous minute foci may represent diffuse myelolipomatosis; on the other hand, a group of fat cells with a dozen "lymphocytes" and a few cells resembling myelocytes should not be called myelolipoma. A regularly convex contour and compression of the surrounding tissue may serve as distinguishing criteria, and generally the diameter of such a lesion will be 4 mm. or more. In a group of such borderline cases, the frequency of irregular adenoma-like cortical nodules was impressive. The most diffuse myeloadipose infiltration was found in a patient with profound endocrine disturbance (diabetes, cataracts, hypotension, and a thecoma of the ovary, AFIP Acc. 719645). The lipid content of the surrounding cortical cells does not differ from that of the cortex in general.

The cells in the myelolipomatous area, other than the hemic and the well defined fat cells, are of bewildering variety, and this, together with the similarity between fat cells and lipid-filled cortical cells, has led to conflicting interpretations. Some areas (Figs. 16, 20) are occupied mainly by elements that approximate the fat cells in size but have a fairly compact cytoplasm. Bands, networks and islands are formed by similar cells of varying sizes and densities, with one thing in common: their nuclei are irregularly round and are not pushed to the periphery as are those of fat cells (Fig. 16). The gussets between some of the fat cells contain single large cells, each with a bizarre nucleus (Fig. 19). In addition, there are cells with obvious degenerative changes, vacuolar and otherwise (Figs. 16, 20), too varied for detailed description or illustration. All of these represent altered adrenal cortical cells.

The vascularization of the myelolipoma is difficult to evaluate, because collapsed capillaries may be unrecognizable. The accumulation of fat in the reticulum may narrow the capillaries by compression or stretching. The vascular channels seem to be less numerous than in the neighboring adrenal cortex, an observation already made by Gierke.[2]

A search for the sources of the bone narrow-like tissue in myelolipoma must take into account its two components, fat cells and blood-forming elements.

The Fat Cells

Fat cells, singly or in groups, often occur in the human adrenal cortex but have received little attention, perhaps because they are not known to be related to disease. Gierke,[2] in describing them, expressed surprise that they had not been mentioned before. Paunz,[14] who studied the adrenal glands in 500 necropsies, observed them "repeatedly." Gossmann[15] noted fat cells, varying from single cells to 15 or 30 in one section, in 21 of 150 glands; they were absent in children, rare in persons less than 40 years of age, but frequent in those more than 70. This increased incidence with advancing age was confirmed by Stieve[16] in a detailed study of 511 adrenal glands from people who had died by violence and in whom there was no evidence of disease at necropsy. He noted that fat cells appeared when the gonads became atrophic under conditions of prison life. In young women who had had amenorrhea for a year or longer, fat cells were fewer than in women more than 35 years of age. These observations were corroborated in the material examined in this study. Furthermore, no fat cells were found in single sections of adrenal from 29 cases of sudden traumatic death of young men.

Little, if anything, seems to be known about the occurrence of fat cells in the adrenal cortex of animals. I found none in one or more sections from several mammalian species (10 chimpanzees, 7 macacus monkeys, 46 cows, 14 sheep and 34 cats). They were present, however, in the adrenals of 2 of 27 dogs and 1 of 2 opossums, and singly or in small groups in 6 of 11 rabbit adrenals studied in series.

The origin of the fat cells in the adrenal cortex is a much debated topic. Single fat cells in a lipid-rich cortex are not conspicuous because they resemble the cortical cells, and some authors have tacitly or expressly assumed that they were transformed cortical cells.[16-20] This is in contradiction to the prevailing idea that the fat cell is a modified reticulum cell[21,22] or, perhaps, a modified fibroblast.[23] The transformation into fat cells of highly differentiated adrenal cortical cells seems as improbable as would such a metamorphosis of parenchymal cells in a severely fatty liver. The cortical cells between the fat cells of the myelolipoma, or between grouped fat cells in the cortex, disintegrate and disappear in the same way as do the epithelial elements in adiposity of the pancreas or parathyroid gland. While lipid-rich adrenal cortical cells may mimic fat cells, the true fat cells can be recognized by a detail of their nucleus, namely, the *Lockkern*. This descriptive

term, coined by P. G. Unna[24] in 1895, means a nucleus with a hole. In most fully developed fat cells, the nucleus is indented by a small lipid droplet, which is continuous with the vacuole that fills the remainder of the cell. Continuity with the larger vacuole is not readily seen in sections; hence, the misleading name. As noted by Omelskyj,[25] the indented nucleus occurs in fat cells in myelolipoma and in the adrenal cortex. It does not appear in lipid-filled cortical cells. In good paraffin sections, the punched-out defect in the nucleus was found almost as easily in the fat cells of myelolipoma as in those of the periadrenal fat, and it was only a matter of prolonging the search to find it in other fat cells scattered through the cortex. The presence of these characteristic nuclei proves that the fat cells of myelolipoma are true fat cells and not transformed cortical elements. Further proof lies in the condition of the cortical cells surrounding the myelolipoma. These often contain little lipid, which would not be the case if the myelolipoma had arisen by fatty transformation from them.

The resulting histologic pattern of the cortex is comparable to that of the adipose parathyroid gland or pancreas, but the presence of myeloid cells or "lymphocytes" in the myelolipoma indicates a biologic difference. Even severe adiposity of parenchymal organs does not lead to the formation of circumscribed lipoma-like structures comparable to the myelolipoma.

The close relationship between fat tissue and hematopoietic tissue has its basis in their common origin from reticulum. The simultaneous or successive appearance of fat and hemic cells would be inexplicable if the fat cells were derived from the cortical cells and not from the reticulum.

The So-called "Lymphocytes"

In searching the adrenal cortex for a source of the blood-forming elements, one automatically considers the cells often present in abundance, for which, unfortunately, no fitting name exists. They have been called lymphocytes,[26] round cells,[14,27] small mononuclear cells, polyblasts, and *cosidette cellule rotonde*.[4] For the sake of convenience, I shall call them "lymphocytes" (which many of them are not). The interpretation and designation of these cells in the literature of 7 decades reflect the changing opinions about origins and relationships of circulating and fixed cells. The paucity of illustrations may indicate uncertainties of interpretation. The idea that these cells stem from the reticuloendothelial cells will hardly be disputed today. They were mentioned as early as 1887,[27] and have been investigated much more than the fat cells, perhaps because they appear alien to the adrenal cortex and supposedly are related to infection. All authors agree that

they are frequent in the adrenals of adults; the incidences given vary from 17 to 100 per cent. Some authors consider their presence in the adrenal normal. E. Thomas[28] found them in 38 of 40 cases, in each of which he examined 50 sections from 6 or 8 blocks. In the 2 cases in which these cells were absent, death was caused by execution in one, and septic tracheitis, probably a disease of short duration, in the other. Stieve[16] found them only in persons more than 50 years of age, except for a few women with amenorrhea between 35 and 50. He found them regularly in old people. I found the "lymphocytes" at necropsy in 77 per cent of 117 adult males at the Veterans Hospital in Topeka. In these, serial sections were prepared from some blocks and single sections from others. They were more frequent in older patients (34 of 41 more than 60 years of age; 9 of 10 more than 75). The number and size of the foci bore no relation to the weight of the adrenals or to the necropsy findings. It may be anticipated here that the incidence in relation to age was the same in the cases of myelolipoma, and as far as one can judge from the literature, this has been the experience of others also. On the other hand, among the 29 cases of sudden traumatic death in which fat cells were not seen in the adrenals, neither were "lymphocytes."

The erroneous belief that these cellular foci were related in some way to infection persisted until recently, in spite of Landau's[29] correct observation in 1915 that they were not associated with infection. The older literature often mentions "heaps of lymphocytes"[30] and their possible relationship to the disease that caused death, but these assumptions do not appear well founded today. The cellular foci were not more frequent in the old necropsy material with its many infectious and septic cases than in that of the last two decades in which chronic noninfectious diseases have been prevalent. Only in cases of sudden death without disease are they absent or rare. This indicates that the cause is not infection but disease in general. One may assume, then, that common disturbances in the organism cause fat cells and "lymphocytes" to appear in the adrenal cortex, while some unknown, uncommon ones result in the formation of myelolipoma.

Information about the occurrence of "lymphocytes" in animal adrenals is contradictory, possibly because of the ill-defined nature of these cells. In the present investigation a few were found in a series of sections of rabbit adrenals and in single sections from cattle and dogs; none were observed in 24 rat adrenals.

Single fat cells or small clusters of them may appear in cortical tissue which is normal except for slight compression of adjacent cells (Figs. 6, 9). Even an isolated fat cell may be accompanied by

"lymphocytes" (Fig. 11), and larger and more compact groups of fat cells often contain considerable accumulations of these elements (Fig. 10). At medium magnification, collections of this nature, with both densely cellular and fatty portions, appear as myelolipomas (Fig. 8), but if the so-called lymphocytes were really lymphocytes, this resemblance would vanish under higher magnifications. However, as the indecisive nomenclature suggests, the pattern of these cells is varied. Ordinary "cellular foci" in adrenals at necropsy often contain cells with abundant cytoplasm and chromatin structure resembling that of myeloid elements (Figs. 14, 17, 23). These cells may show cytoplasmic granulations when stained with Giemsa stain. Some cells with very compact nuclei probably represent erythroblasts, and origin from sinusoidal lining cells is suggested by dark-staining, swollen endothelial nuclei (Fig. 14). The conviction that such myeloid elements originate *in situ* becomes firmer from careful study of microscopic sections than from viewing a limited number of illustrations.

Incidence

The myelolipoma is not such a rarity that every single case will find its way into the literature. Thus, its incidence cannot be truly gauged from reports which are available. McDonnell,[31] who reported 4 cases, gives an incidence of 0.2 per cent for a series of 2,000 necropsies, which probably included children and infants. Mattei's[5] 5 "adrenal lipomas" occurred in 1,951 necropsies. Biressi[4] in 1954 listed 54 cases, some of which, in my opinion, were not myelolipomas but represented bone marrow formation within ectopic bone.[32-36] Bone marrow within bone does not belong in the category of myelolipoma. Ossification occurs in the adrenal gland, notably after hemorrhages and after necrotizing and chronic inflammatory processes. The fact that such lesions have been called myelolipomas[24,27] creates confusion. Generally it is easy to distinguish between bone that contains marrow and a mass of myeloid tissue that has formed a few spicules of bone. The two reported myelolipomas in infants[25] represented bone marrow within bone. It is important to remove these two cases from the category under discussion because, so far, true myelolipoma has not been observed before puberty. The case of Vera Hirschfeld, which appears in the lists of Biressi[4] and others, cannot be verified (Hirschfeld's paper does not mention it[28]).

The youngest patient with myelolipoma in the AFIP series was 17 years old, the oldest 93. Twenty-seven of the 50 were in the fifth and sixth decades; 33 were between the ages of 46 and 65; 39 between the ages of 36 and 65. When these figures are compared with the death

rates for different age groups of adult males (U. S. census for the year 1950), the occurrence of myelolipoma appears as 1 in 7,600 for the age group from 36 to 65, with practically no difference between these three decades, while the frequency for all other decades is 1 in 41,000. There is no way of determining how long a myelolipoma found at necropsy has taken to develop.

There was no correlation between the myelolipoma and disturbances of the hematopoietic apparatus, despite the resemblance to bone marrow. The 50 cases from the AFIP included only one instance of leukemia and one of doubtful hyperplasia of bone marrow. The relative frequency of the diseases accompanying myelolipoma was not unusual. Nine cases of cirrhosis of the liver are perhaps more than should be expected, but I have observed a similar preponderance of cirrhosis in obviously unrelated lesions such as focal arteritis and pituitary necrosis.

There was no indication of a relationship to hypertension.

Endocrine Correlations

Twenty-eight of the 50 patients studied were obese, 11 of them severely so. The frequency of obesity appears even more striking when one considers the 22 cases in which the diameter of the myelolipomas was 1 cm. or more. Of these 22 patients, 15 were obese, 7 severely so. This predominance of obese patients might lead one to suspect an alteration of fat metabolism.

Significant endocrine disturbances were present in 9 of the 100 cases. Auvray[39] found large bilateral myelolipomas in a 72-year-old pseudohermaphrodite who had small internal sex organs, no vagina or vulva and a large, partly perforated clitoris. A schizophrenic female intersex, 58 years of age, also had large bilateral myelolipomas.[40] Bilateral myelolipomas (size not given) were found in a 49-year-old man with severe pluriglandular disease.[41] Four weeks after removal of a "fist-sized" adrenal adenoma, a young woman who had become virilized was normal again and menstruated.[42] This adenoma, which is not described in detail, contained much bone marrow. Sternberg,[43] without giving details, mentioned a myelolipoma in a contracted adrenal, and Paul[26] found a myelolipoma the size of a pigeon's egg in a woman who for one year had shown the classical symptoms of Addison's disease. In two instances,[44,45] myelolipomas were associated with extreme obesity, splanchnomegaly without acromegaly, and sudden death. The "adenoangiolipoma" which Letulle[46] observed in a hermaphrodite obviously must have been, at least in part, myelolipomatous. I would not draw the conclusion from these cases that myelolipoma

exerts an endocrine influence, but I believe that the adrenal cortex, in the presence of severe endocrine disturbance, is more likely to react with the formation of myelolipoma. The possibility of participation in a clinical syndrome is shown, however, by the cases of Schmidt[44] and of Plaut[45] cited above. A diffuse infiltration of the adrenal cortex by fat cells and myeloid elements may fall into a similar category (male, 39 years, severe Cushing's syndrome, AFIP Acc. 727046). It should be noted also that 3 of the 8 patients with bilateral myelolipomas had severe endocrine disorders: one intersex,[40] one pseudohermaphrodite,[39] one man with pluriglandular insufficiency.[41]

Pathogenesis

The life history of the myelolipoma is unknown. It has not been found before puberty, but appears with increasing frequency in older age groups. It is not known in what phase it is more fatty or more myeloid. Oberling[3] thought that the myelolipomas which were predominantly fatty represented the older lesions, but the study of many cases has convinced me that the fat cells may just as well precede the hematopoietic elements.

While attempting to understand the presence of myeloid cells in the adrenal cortex, one wonders whether such cells are found there in the wake of definite diseases or injuries. The only instance encountered is death after burning. Delarue and Monsaingeon[18] have found "*des îlots myeloides indiscutables*" in 3 of 8 burn victims; these 3 had died between 3 weeks and 3 months after the accident. The myeloid cells, in places, were close to fat cells, and a fine reticulum "completed the analogy with bone marrow tissue." The authors did not succeed in reproducing this adrenal lesion in the rat or the rabbit.

The adrenal glands from 22 of the 23 nonseptic burn cases were not unusual; the fact that necrosis and thrombosis were seen in one is not astonishing.[47] The adrenal of one case, however, was remarkable. The patient, a 20-year-old pregnant woman, died 8 days after a gas explosion which had burned 80 per cent of her body surface. The leukocyte count on admission was 10,150, but on the sixth hospital day it had fallen to 2,400. On the following day it rose again to 11,150. The bone marrow at necropsy showed slight hyperplasia and maturation arrest, consistent with early agranulocytosis. Myeloid reaction was slight in the liver and spleen but severe in the adrenal cortex. This may have been caused by the same unknown factors that were operative in the 3 burn cases cited above.[18] Gormsen[48] observed a similar distribution of hematopoiesis in a woman who had died of anemia from metrorrhagia.

Formation of fat tissue and hematopoiesis may occur simultaneously, not only in the embryo and in bone marrow, but also in organs of the adult under conditions other than anemia or infection.[49-53] The one well established point in the etiology of the myelolipoma is that its precursors, the cortical fat cells and "lymphocytes," are absent in persons killed while in good health. No significant correlation with a single disease exists. The fact that in 3 instances the myelolipoma contained foreign bodies suggests the possibility of local trigger mechanisms.[54] Injection of fat tissue juice into the adrenal cortex of rabbits, and implantation of a piece of omental fat, with its blood supply preserved, into the adrenal of a dog did not result in formation of fat cells or hemic cells.*

The question of how far the functional activity of the adrenal cortex can influence the formation of myelolipoma can hardly be answered by the study of routine sections. Cortical nodules seldom accompanied a circumscribed myelolipoma; they were more often found in conjunction with diffuse myeloadipose or myeloid infiltration. In animals, myeloid cells have occasionally been limited to cortical adenomas. In man, in the absence of myelolipoma, only a few myeloid cells appear in the adrenal cortex; one must hunt for these among the "lymphocytes."

In the adrenal cortex of man and probably of the rabbit, fat cells predominate over myeloid cells, while the reverse obtains in the dog and in cattle. Such observations reflect the labile balance between fat tissue and hematopoietic tissues.

Related Extra-adrenal Structures in Man

Finally, the question arises as to how far the adrenal myelolipoma is related to similar tumor-like bone marrow structures occasionally found in retroperitoneal or retropleural tissues.[55-66] They have not been seen in the places in which ectopic nodules of adrenal cortex are frequent, namely the broad ligament and the spermatic cord. Assuming that some general condition was responsible for the formation of the ectopic structures resembling bone marrow, one would expect such lesions to accompany myelolipoma, but in only 1 out of 14 cases of this nature is an adrenal myelolipoma mentioned, and that a small one.[61] One of these case reports includes a statement that the adrenal gland was normal; the others do not mention it.

In 4 of 12 cases,[55-66] the hematopoietic system was normal and there was no anemia; in 3 there is no statement about anemia; in 2 there was carcinoma with anemia; in 2, pernicious anemia; and in 1, partial

* Experiments carried out with R. M. McCully.

osteosclerosis (but no mention of blood findings). These bone marrow-like structures thus are more often associated with anemia than is the case with myelolipoma, and this indicates that some of the conditions which lead to adrenal myelolipoma must be looked for in the adrenal cortex itself. The sex distribution is significantly different from that of myelolipoma, since 13 of the 14 patients were female.

Tentative Classification of Myeloadipose Structures

Three entities should be kept separate: the myelolipoma, extramedullary hematopoiesis, true bone marrow.

The myelolipoma consists of myeloid cells and fat cells and contains reticulum only in the fatty portions (Figs. 21, 22). The absence of reticulum and sinusoids stamps the myelolipoma as something different from bone marrow, a fact not to be overlooked in spite of the apparent similarity. Since the myeloid cells are not situated in reticular sinusoidal structures, it is hard to see how blood cells formed in such an area can enter the general circulation. Certainly there can be no controlled releasing and holding mechanisms as in normal bone marrow.

Extramedullary hematopoiesis consists of myeloid cells without fat cells. As far as I can judge, no reticulum is formed in such areas, and, in large foci at least, pre-existing reticulum may be destroyed. The simple fact that in extramedullary hematopoiesis bone marrow is not formed[48] should always be kept in mind.

True bone marrow occurs in the adrenal gland when calcification has led to bone formation. Its reticulum is like that of normal bone marrow.

Conclusions and Summary

Myelolipoma of the adrenal cortex, although recognized for half a century, remains unexplained. It has been found only in man. It consists of adult white fat tissue and varying numbers of hemic cells. Some of the latter are myeloid elements, others resemble lymphocytes. The lesion occurs most frequently in middle life, has no sex predilection, and has not been described before puberty. It bears no relation to anemia or other disturbances of the hematopoietic system and has nothing to do with compensatory extramedullary hematopoiesis. It has no relation to any single disease, and no single endocrine influence is known. The fact that a number of patients, notably with large and bilateral myelolipomas, had severe endocrine disturbances suggests that the abnormal adrenal cortex may be more prone to form myeloadipose structures.

The simultaneous or alternating formation of fat cells and hematopoietic cells from the reticulum of the adrenal cortex might be analogous

to processes which occur during embryonic development, but the myeloadipose structures do not stem from embryonic rests. In the myeloid portions of the myelolipoma the reticulum is destroyed. Thus, it cannot be said that the myelolipoma is bone marrow; it merely resembles it.

The myelolipoma represents a local intensification of a more diffuse process which is present at necropsy in the adrenals of a high percentage of adults, namely, diffuse or focal infiltration by fat cells and "lymphocytes." These, however, are absent or very sparse in the adrenals of people who have been in good health before death, and thus represent a reaction to disease in general, without relation to a single disorder or group of disorders. The assumption that they are caused by infection is disproved by statistical studies which show that the lesions are no less frequent in the necropsies of today than they were decades ago when infectious diseases were much more prevalent. The absence of fat cells and hemic cells in the adrenals of healthy people and their almost equal frequency in a wide variety of diseases point to general causative factors. There must be a link between disease in general and the tendency of the reticulum of the adrenal cortex to form fat and hemic cells.

The adrenal cortical cells in the area of the myelolipoma disintegrate and disappear in the same way as do epithelial cells in adiposity of other parenchymal organs. Cortical cells are not transformed into true fat cells. The true fat cells in the adrenal cortex, as elsewhere, can be recognized by the characteristic indented nucleus, the *Lochkern*.

Myelolipoma in animals has not been recorded. That the myeloid cells in the adrenal cortex of animals represent a related phenomenon is a matter of speculation. Masses similar to bone marrow, found in retroperitoneal or retropleural regions, differ from myelolipomas by their association with blood disorders, especially anemia, and by their apparent limitation to the female.

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[*Illustrations follow*]

LEGENDS FOR FIGURES

All illustrations are from men (or animals) without known hematologic disease or important infection. Illustrations were made from sections stained with hematoxylin and eosin unless stated otherwise.

FIG. 1. AFIP Acc. #633142, Neg. 55-8768. Spherical myelolipoma, 1 cm. in diameter. The myelolipoma has the gross appearance of lipoma unless myeloid tissue is abundant or there is hemorrhage. Gross specimen. × 2.

FIG. 2. AFIP Acc. #629321, Neg. 56-8712. A myelolipoma which obviously has expanded evenly in all directions. × 4½.

FIG. 3. AFIP Acc. #196568, Neg. 55-16455. A 7 mm. nodule consisting almost entirely of cellular marrow. The surrounding cortical tissue appears considerably stretched. × 10.

FIG. 4. AFIP Acc. #721469, Neg. 56-9457. A mostly myeloid myelolipoma situated between the layers of the capsule. × 9½.

FIG. 5. AFIP Acc. #323582, Neg. 55-12865. Cortical tissue protrudes deeply into the periadrenal fat tissue, which contains two round, partly myeloid, partly fatty, areas of myelolipoma and a less distinct, diffuse cellular infiltration. There is no myelolipoma within the normal boundaries of the adrenal cortex. × 10.

FIG. 6. Four partly confluent fat cells in adrenal of an adult female rabbit. They were the only ones in a large area of cortex. × 185.

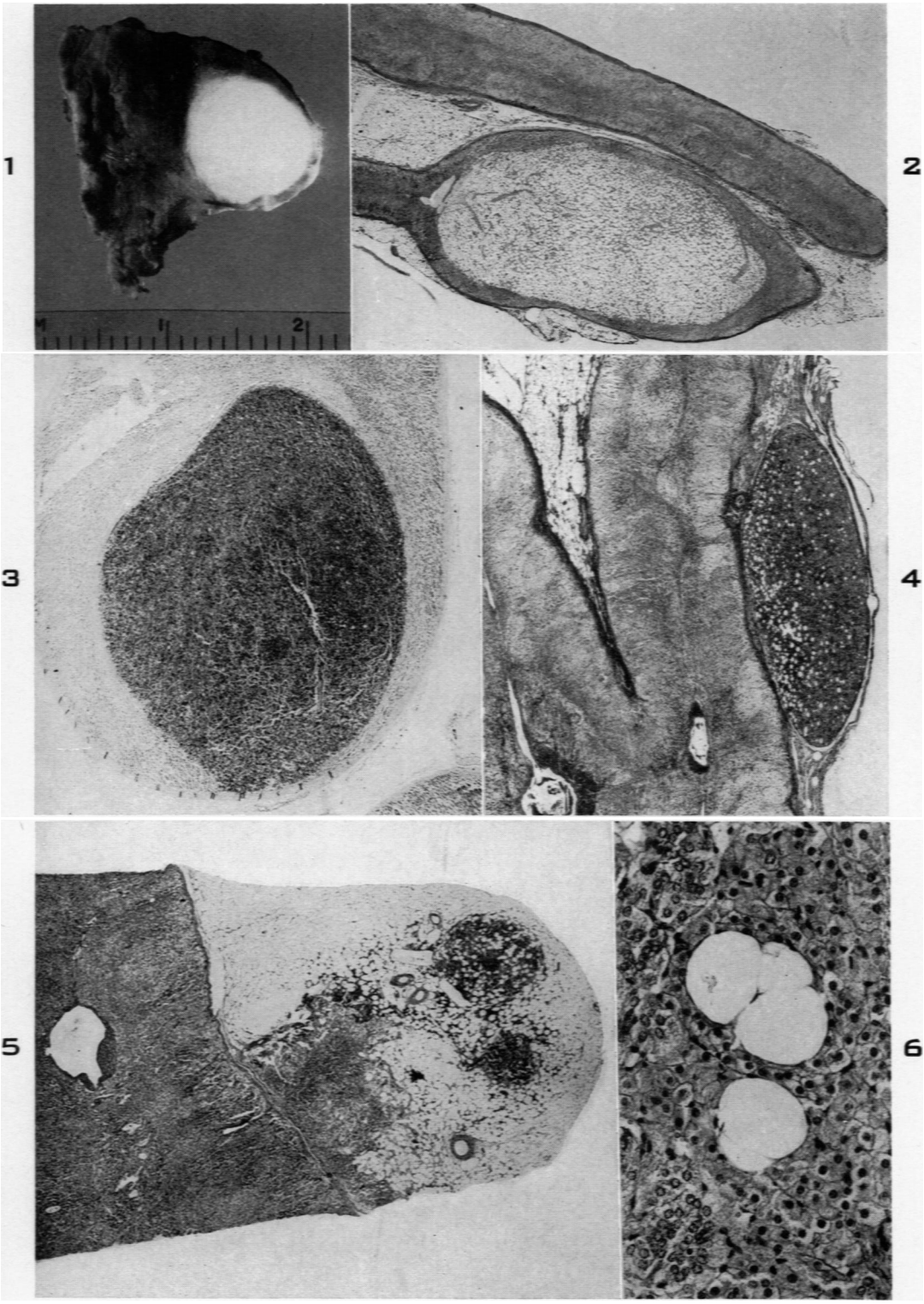

FIG. 7. AFIP Acc. #724046, Neg. 56-22521. A myelolipoma-like area and also diffuse infiltration by fat cells. Other cellular elements cannot be recognized at this magnification. × 9.

FIG. 8. AFIP Acc. #665671, Neg. 5156-2461. A fatty and cellular area resembling myelolipoma. × 90.

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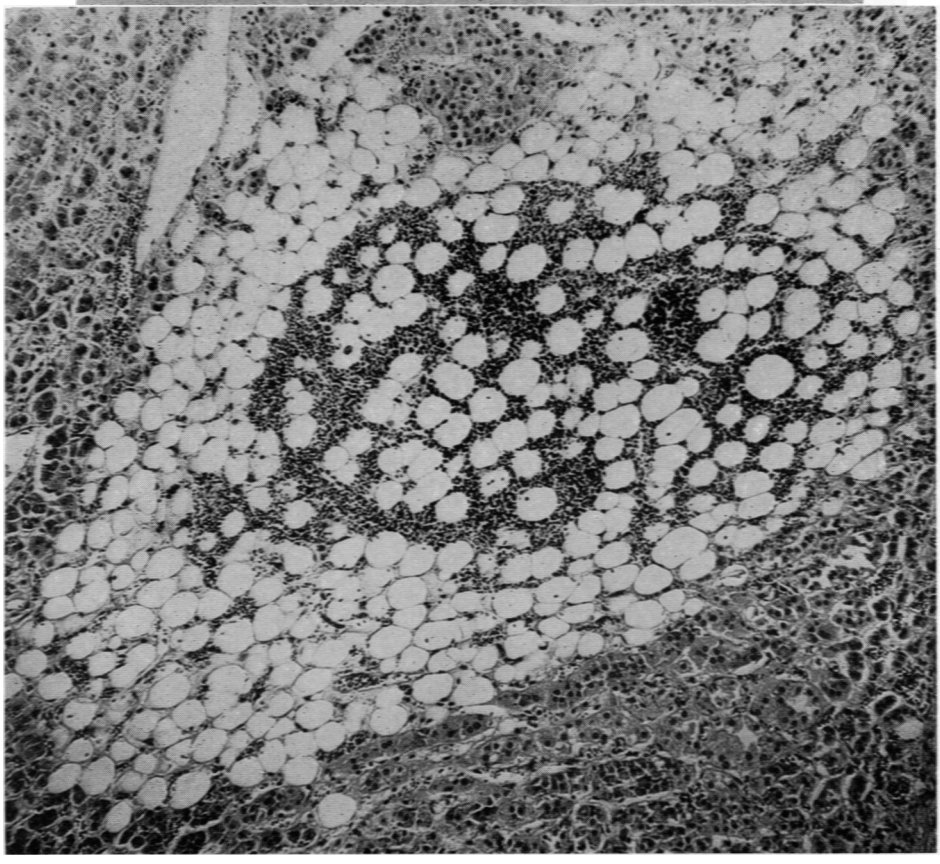

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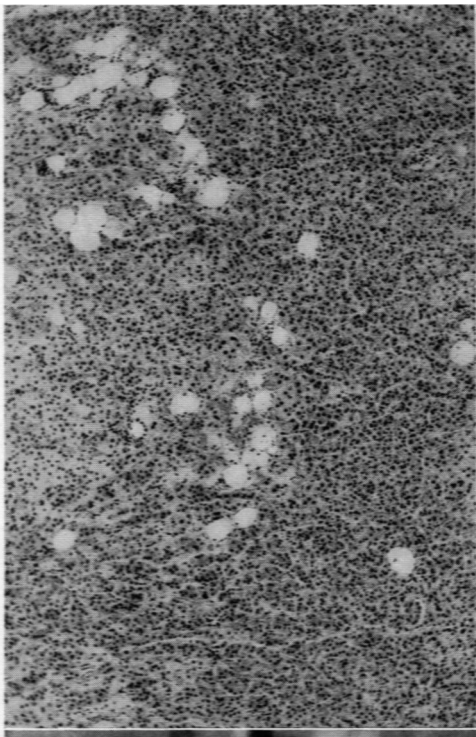
FIG. 9. Scattered and grouped fat cells. × 55.

FIG. 10. AFIP Acc. #727046, Neg. 56-22519. A larger but still discontinuous aggregation of fat cells and "lymphocytes." × 40.

FIG. 11. AFIP Acc. #665617, Neg. 56-11881. A large single fat cell. It was the only one in a large area of normal cortex. A cortical cell has been compressed into a narrow crescent at one margin. Small cells resembling lymphocytes are situated at the opposite margin. The larger of the two dark nuclei in a sinusoid to the left of the fat cell is probably in a myeloid cell. × 650.

FIG. 12. AFIP Acc. #640890, Neg. 56-9154. The diagonal line corresponds to the capsule of the adrenal which separates a myelolipoma from periadrenal fat. The curved row of 5 cells represents a remnant of cortex. Such patterns, especially when complicated by hemorrhage, are difficult to interpret. × 235.



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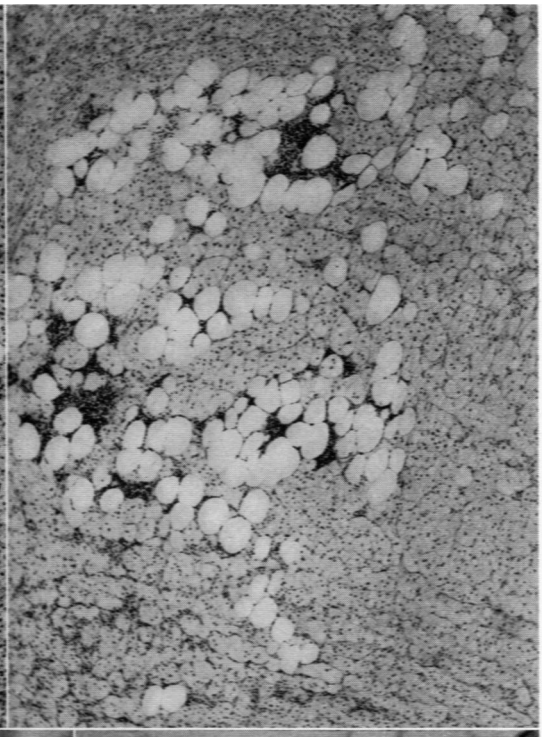

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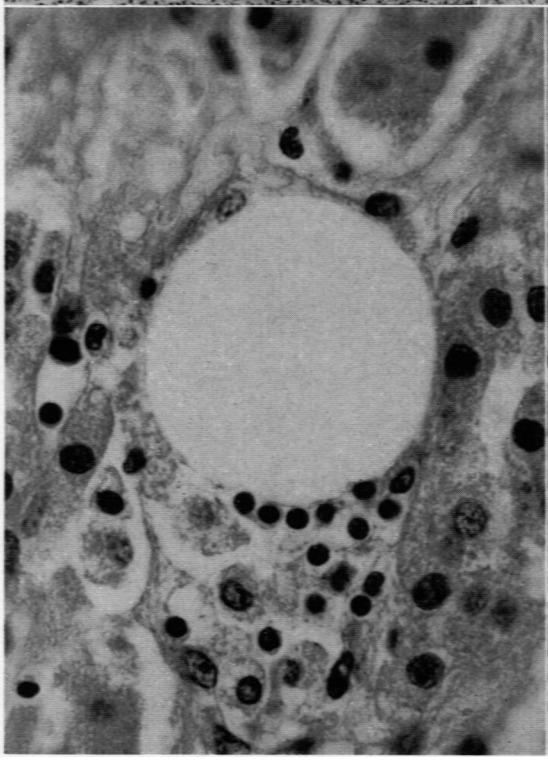

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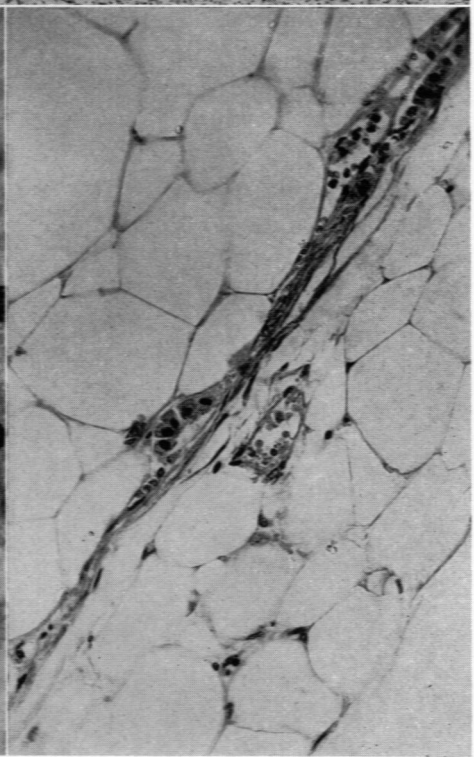

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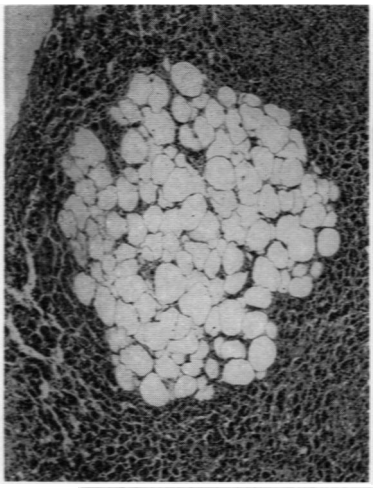
FIG. 13. AFIP Acc. #489929, Neg. 56-23604. A fairly well circumscribed accumulation of closely packed fat cells, perhaps a small myelolipoma. × 42.

FIG. 14. AFIP Neg. 56-5698. Myeloid cells in lumen of an adrenal cortical sinusoid of a rabbit. Note the swelling and intense staining of one sinusoidal lining cell. × 1,300.

FIG. 15. AFIP Acc. #360763, Neg. 55-7732. A centrally located myelolipoma. The round portion on the left is almost entirely fatty. The crescent-shaped darker area on the right contains degenerating cortical cells and myeloid cells. × 4.

FIG. 16. AFIP Acc. #647466, Neg. 55-9923. The large cells, some confluent, containing multiple fat droplets, have large, dark-staining nuclei which are not flattened against the periphery. These represent degenerating cortical cells. × 430.



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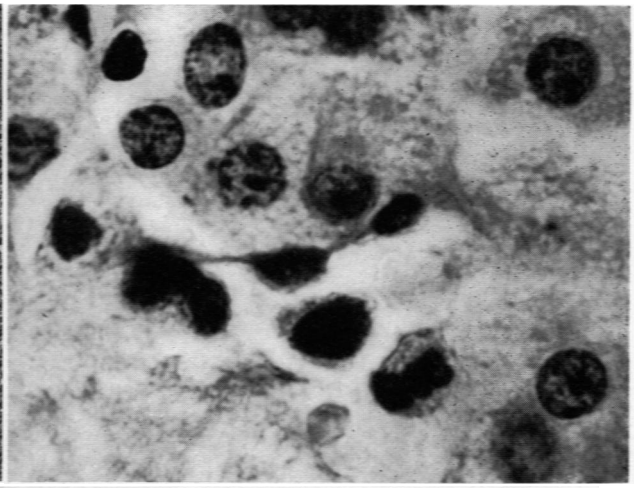

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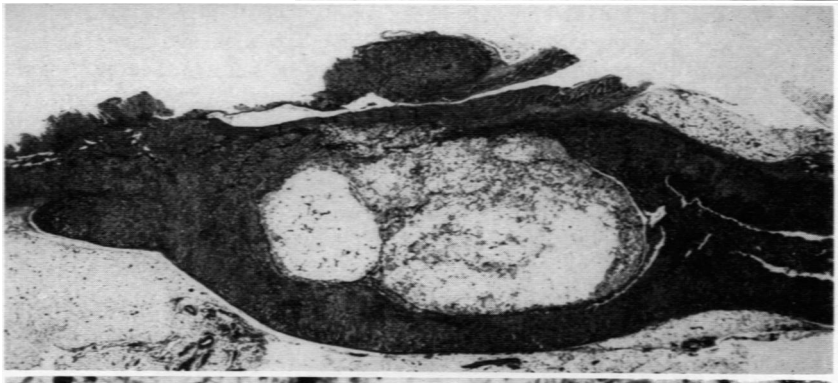

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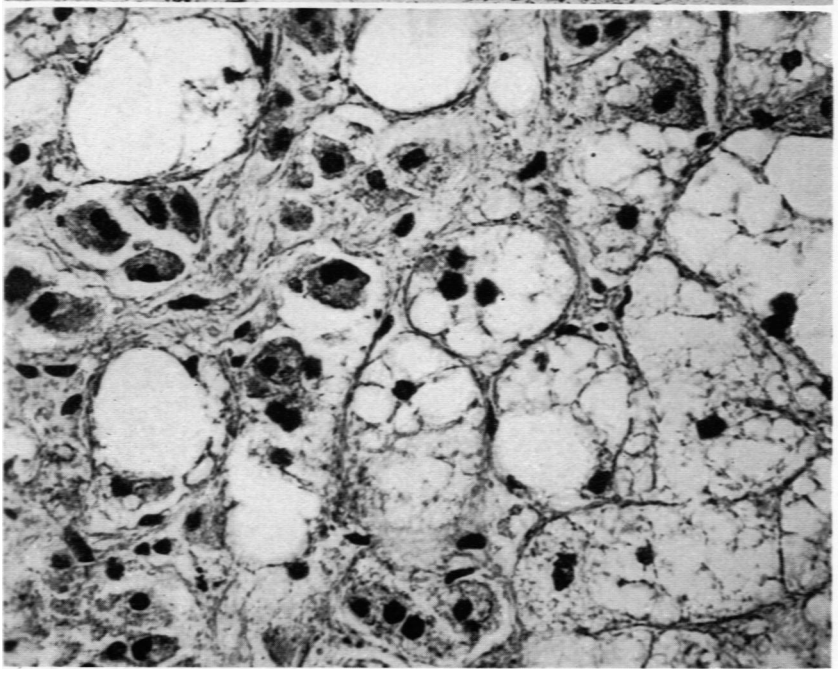

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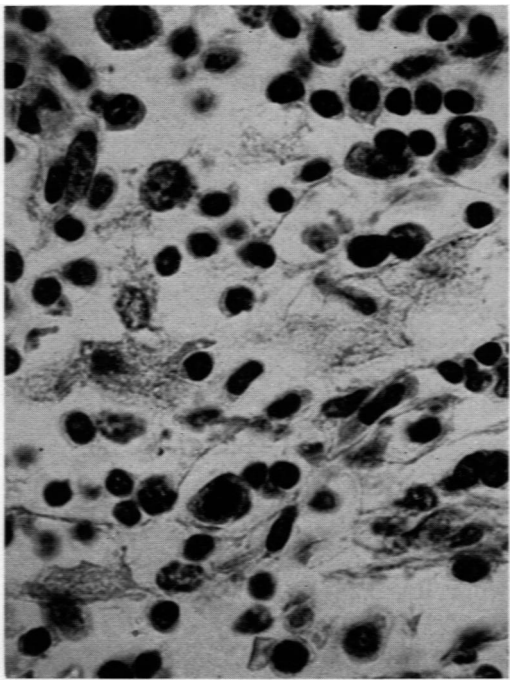
FIG. 17. Autopsy #29, 1951, V. A. Hospital, Topeka. AFIP Neg. 55-7251. While most of the cells resemble "lymphocytes," two are large and have irregular pyknotic nuclei, probably in prophase. They are best interpreted as myeloid elements. × 750.

FIG. 18. AFIP Acc. #649108, Neg. 56-17507. Megakaryocytes in a sinusoid of an adrenal cortical adenoma of a 14 year old dog. There were also other myeloid cells, but the cortex itself contained none. × 550.

FIG. 19. AFIP Acc. #611716, Neg. 55-8687. Bizarre, large nuclei in two degenerating cortical cells which are surrounded by fat cells. × 540.

FIG. 20. AFIP Acc. #560763, Neg. 55-7907. The broad, oblique band with the dark nuclei consists of cortical cells. At the upper right are characteristic fat cells, and at the lower left large granular cortical cells with remnants of nuclei. Such fields give the incorrect impression that cortical cells are transformed into fat cells. × 260.



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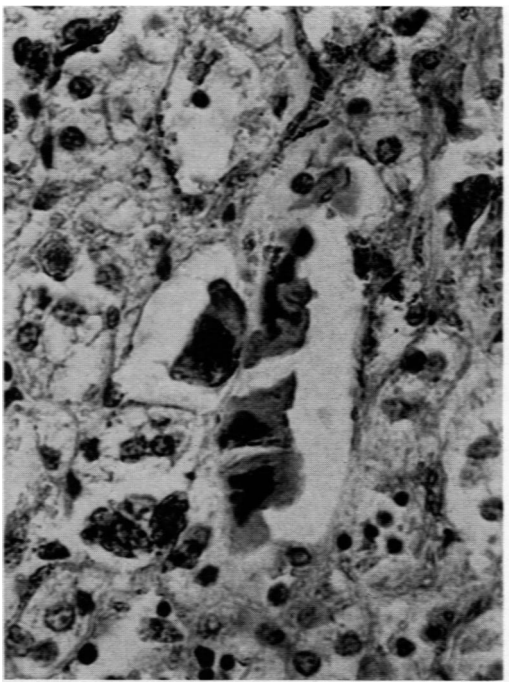

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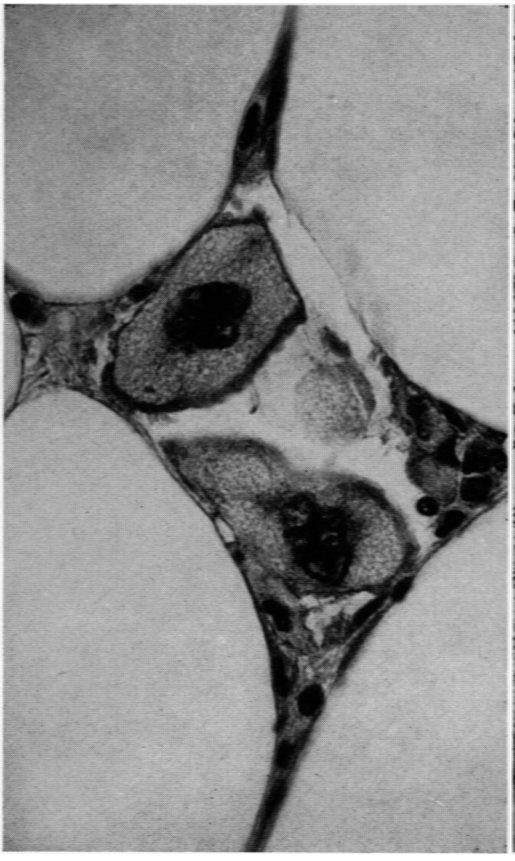

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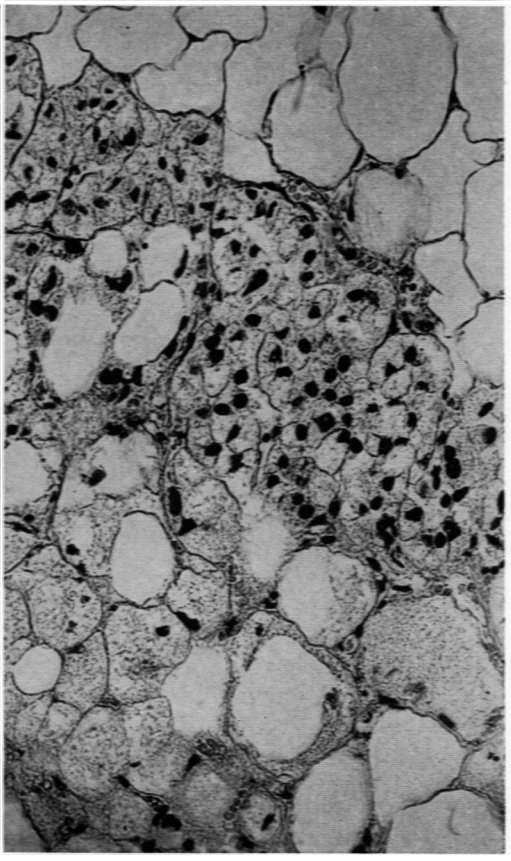

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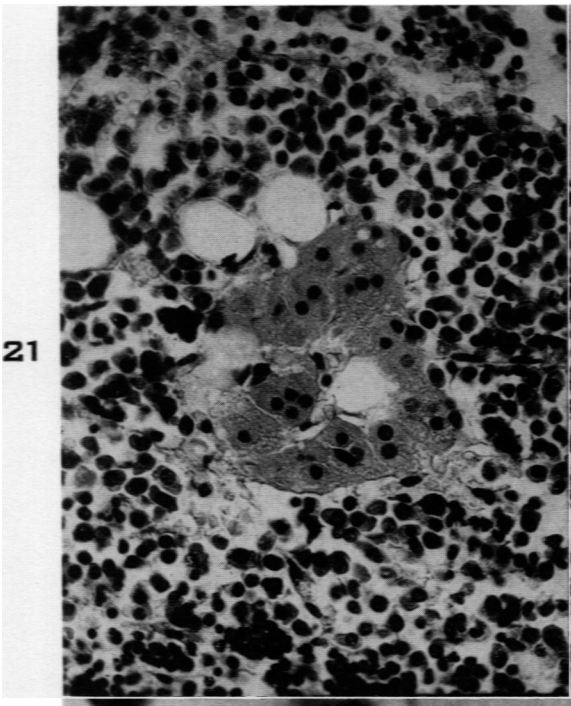
FIG. 21. AFIP Acc. #196568, Neg. 55-20568. A small island of well preserved cortical cells surrounded by myeloid elements of a myelolipoma. × 280.

FIG. 22. AFIP Acc. #196568, Neg. 55-20567. From a neighboring section. Wilder's stain for reticulum. The reticulum in the small island of intact cortical tissue is preserved but is missing in the surrounding myeloid area. × 280.

FIG. 23. AFIP Acc. #582504, Neg. 5154-1252. An area in an ordinary so-called cellular focus in adrenal cortex. The cells vary greatly in appearance and the designation "lymphocytes" does not seem appropriate. It is not possible to put a definite name on each cell. Some resemble plasma cells. × 1,700.



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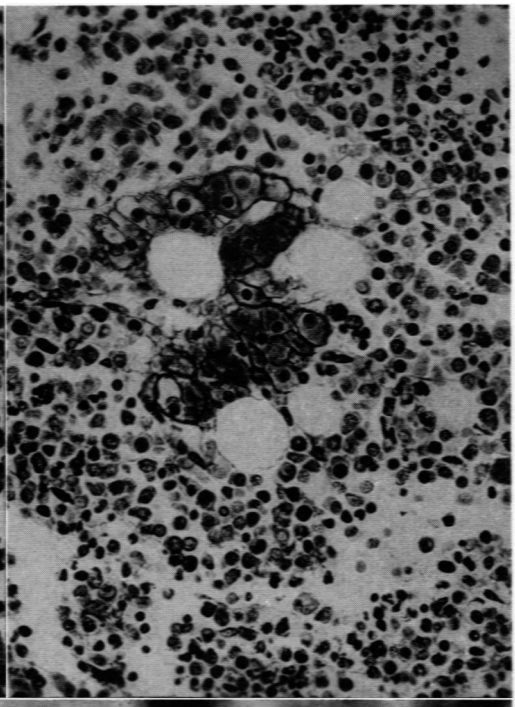

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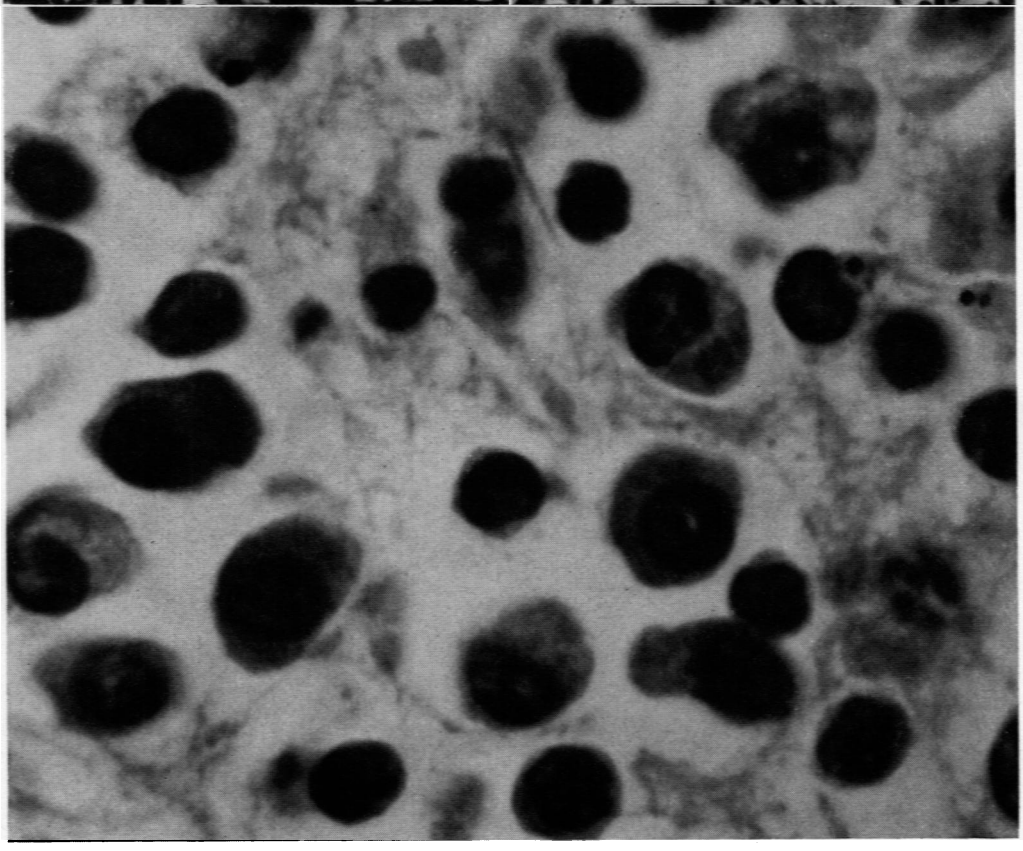

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