CIRRHOSIS AND OTHER HEPATIC LESIONS PRODUCED IN DOGS BY THYROIDECTOMY AND BY COMBINED HYPOPHYSECTOMY AND THYROIDECTOMY

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Plates 1 to 4

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Recent investigations have so focussed interest on the importance of dietary factors in the experimental production of fatty and cirrhotic livers that the significance of endogenous mechanisms in the pathogenesis of such liver disease has hitherto not been fully investigated. It is of interest, therefore, to report that fatty and cirrhotic livers can be induced in dogs deprived of both pituitary and thyroid glands even though they are made to ingest a diet rich in protein and adequate in all other respects.

The primary object of this paper is to present the pathological reactions encountered in the livers of a group of dogs subjected to thyroidectomy alone (T dogs) and to both hypophysectomy and thyroidectomy (HT dogs).[1] However, the pathological material acquired during these experiments also provided an opportunity for studying the pathogenesis of two histologically distinct forms of hepatic cirrhosis, namely that initiated periportally and that which originates in relation to the radicles of the hepatic veins. The occurrence of these two pathologically distinct forms of cirrhosis in animals treated in an identical manner was regarded as unusual enough to merit comment on their pathogenesis, with particular reference to the relationship between long standing fatty change and the onset of liver cirrhosis.

EXPERIMENTAL

The operative procedures employed for excision of the thyroid and pituitary glands, as well as the care and dietary treatment accorded the dogs both before and after operation, have been fully described elsewhere (1–3). In all dogs with two operations (HT) the hypophysis was

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[1] A preliminary report on the development of cirrhosis in the livers of dogs deprived of both pituitary and thyroid glands appeared in the *Proceedings of the Society for Experimental Biology and Medicine*, 1943, **54**, 170.

removed first, and the thyroid gland was resected at variable intervals thereafter. The diets consumed by the animals were adequate in regard to calories, proteins, salts, and vitamins (1–3). The dietary treatment of all dogs and the weight changes that occurred during their stay in the laboratory are summarized in Tables I and II. In all dogs with the two operations (HT), except HT11, appetite was lost after removal of the second gland. The exact caloric intake recorded for all dogs was maintained, when necessary, by forced feeding.

The completeness of hypophysectomy and the absence of hypothalamic lesions were established in all dogs at necropsy.

Thyroidectomized Dogs (T Dogs, See Tables I and III)

The most prominent lesion in the livers of this group of 8 animals was a pronounced fatty change. The liver cells toward the central veins were most severely affected, although in the majority of livers fat was visible throughout the lobules. Toward the portal tracts the fat tended to occur as multiple, varying sized, intracellular droplets, whereas in the centers of the lobules large single globules of fat virtually filled the cell and compressed the residual cytoplasm and nucleus to one side of the cell in the manner usually encountered in very fatty livers.

In addition to the fatty change, two other reactions of interest were noted. Firstly, in all of the animals an infiltration of plasma cells, lymphocytes, and polymorphs was observed, most frequently in the region of the central veins. This cellular infiltration, when marked and centrally located in the lobules, was often associated with a thickening and increased basophilia of the reticulum surrounding the individual enlarged fatty liver cells, apparently identical with that described by Lillie *et al.* (4) and by Costero and Barroso-Miguel (5). In some lobules elongated fibrocytic-cell nuclei were scattered in areas having thickened reticular fibers. This reaction, though not regarded as cirrhosis, can, in the light of the evidence presented below, be regarded as heralding a fibrosis. The second reaction worthy of record was the occurrence of fairly well marked edema and cellular infiltration around the sublobular divisions of the hepatic radicles.

Cirrhosis, of the severity described below, was not detected in the liver of any animal in this group of thyroidectomized dogs.

Dogs with Both Hypophysis and Thyroid Removed (HT Dogs, See Tables II and IV)

Fatty changes of varying severity were observed in the livers of 8 of the 9 dogs in this group. The livers of 4 animals were severely cirrhotic, while in 3 other animals early fibrosis of varying severity was present; in two of these 3 the normal lobular arrangement was for the most part retained, and consequently the changes were regarded as pre- or mildly cirrhotic rather than as frankly cirrhotic.

Fatty Change.—In 4 dogs the fat occurred as large globules in most of the

liver cells throughout the lobule. In the 4 animals in which some of the liver cells had escaped fatty metamorphosis, it was the cells toward the periphery of the lobules that were unaffected. Thus in Fig. 1 the dilated hepatic radicles are surrounded by enlarged fat-containing liver cells, while the zone of cells bordering on the portal tracts is rather mildly affected by the fatty change.

TABLE I

Dietary Treatment and Weights of Thyroidectomized Dogs

Dogs	Condition	Interval of observation	Dietary treatment*	Weight ranges		
				T2	T5	
		days		*kg.*	*kg.*	
	Before thyroidectomy	11	30 gm. meat and 5 gm. sucrose per kg. per day	7.9–8.3	9.6–9.9	
	After "	1–65	Same as preoperative diet	9.0–10.0	11.0–12.7	
	" "	66–116	Alternate fast (5 days) and refeeding (5–12 days)	9.0–10.0	11.7–12.5	
T2 and	" "	117–236	15 per cent of preoperative diet	7.0–9.0	9.0–11.7	
T5	" "	237–394	Alternate fast (5 days) and refeeding (5–11 days)	7.6–8.1	9.9–10.4	
	" "	395–799	Same as preoperative diet	7.0–12.7	9.5–13.2	
T7	Before thyroidectomy	32	30 gm. meat and 5 gm. of sucrose per kg. per day	8.5–8.6		
	After "	387	Same as preoperative diet	8.6–9.8		
				T12	T14	
	Before thyroidectomy	20	30 gm. meat and 5 gm. of sucrose per kg. per day	9.2–9.6	12.4–13.0	
T12 and	After "	1–20	Same as preoperative diet	9.7–10.1	13.2–14.6	
T14	" "	20–192	Alternate fast (5 days) and refeeding (5–7 days)	10.0–11.5	12.0–18.2	
	" "	193–460	Same as preoperative diet	11.2–12.5	11.4–18.2	
				T16	T17	T19
T16, T17, and T19	Before thyroidectomy	15	30 gm. meat and 5 gm. of sucrose per kg. per day	8.7–9.0	8.1–8.5	9.0–9.2
	After "	300	Same as preoperative diet	9.0–9.2	8.5–9.4	9.0–9.8

* In addition to the dietary constituents listed above, each dog also received daily vitamin and salt supplements. A more detailed description of the treatment of these dogs will be found in previous publications (1, 2)

The severest fatty changes were detected in those livers classified as showing early fibrosis, and in these cases the cellular infiltration and fibrotic changes described and portrayed below occurred in and around the enlarged fatty liver cells in the central portions of the lobules (Figs. 2 to 5). The less severe fatty changes were present in those livers which were quite free of fibrosis, and also in the most severely cirrhotic livers.

Occasionally, in the livers free of fibrosis, round cell and polymorphonuclear

TABLE II

Dietary Treatment and Weights of Hypophysectomized-Thyroidectomized Dogs

Dogs	Condition	Dietary treatment*			Weight range
		Interval	Meat	Sucrose	
		days	*gm. per day*	*gm. per day*	*kg.*
	Before hypophysectomy (H)	73	220	44	8.5– 9.1
HT3	After H	58	220	44	9.0–11.0
	After H and thyroidectomy	97	220	44	10.6–11.2
	Before hypophysectomy (H)	72	270	54	9.4–10.2
HT6	After H	56	270	54	10.0–11.2
	After H and thyroidectomy	135	270	54	11.2–15.3
	Before hypophysectomy (H)	75	250	50	8.0– 8.8
HT8	After (H)	47	250	50	8.5–10.3
	After H and thyroidectomy	419	250	50	10.0–16.5
	Before hypophysectomy (H)	69	260	52	8.6– 9.7
HT10	After H	59	260	52	9.3–11.8
	After H and thyroidectomy	398	260	52	11.5–20.6
	Before hypophysectomy (H)	8	180	36	6.0– 6.6
HT11	After H	49	180	36	6.6– 7.5
	After H and thyroidectomy	374	180	36	7.3–12.5
	Before hypophysectomy (H)	36	325	10	10.2–10.7
HT18	After H	36	325	10	10.3–12.3
	After H and thyroidectomy	250	325	10	12.9–18.0
	Before hypophysectomy (H)	37	260	10	7.7– 7.9
HT21	After H	45	260	10	7.3– 8.0
	After H and thyroidectomy	217	260	10	7.6–14.5
	Before hypophysectomy (H)	12	270	10	8.3– 8.5
HT22	After H	45	270	10	8.1– 8.7
	After H and thyroidectomy	311	270	10	8.8–19.7
	Before hypophysectomy (H)	35	300‡	100	6.5– 6.8
	After H	47	300‡	100	6.5– 9.1
	After H and thyroidectomy	68	300‡	100	8.7–12.3
HT15	" " " "	43	150‡	50	12.0–12.1
	" " " "	71	54‡	10	9.7–12.1
	" " " "	36	36‡	6	9.0– 9.7
	" " " "	47	150‡	50	9.0–11.5
	" " " "	25	0	0	9.0–11.5

* In addition to the dietary constituents listed above, each dog also received daily vitamin and salt supplements. A more detailed description of the treatment of these dogs will be found in a previous publication (3).

‡ Dog HT15 received throughout ground fish instead of lean meat.

TABLE III

Pathology of Liver of Thyroidectomized (T) Dogs

Dog	Sex	Time after thyroidectomy when sacrificed	Liver weight	Fatty acids in liver	Histological fat in liver	Hepatic fibrosis	Hepatic cirrhosis	Round cell infiltration in liver
		days	*gm.*	*per cent*				
T2	F	799	432	21.5	5+; droplets and globules; PSL*	0	0	Scattered foci
T5	F	799	431	22.7	2-3+; mainly globules; PSL patchy	0-2+; very patchy and mainly in subcapsular fatty lobules	0	PSL
T7	M	387	201	5.9	Small foci of PSL globules	0	0	PSL
T12	F	460	417	21.7	5+; PSL droplets and globules	0	0	PSL edema
T14	M	460	419	20.2	2-3+; mainly droplets, some globules; PSL and PP‡	0	0	PSL edema
T16	M	300	253	6.6	2+; scattered globules; not in all lobes	1+; scattered but mainly PP not related to patchy fat	0	Scattered foci
T17	F	300	187	7.8	2+; scattered globules not in all lobes	1+; mainly in central fat and very patchy	0	Foci among fatty cells
T19	F	300	252	11.5	1-5+; globules, much variation in same section and in different lobes	0-3+; very patchy, mainly in very fatty subcapsular lobules, much variation in different lobes and even in same section	0-1+; very patchy varying markedly in same section and in different lobes	Focal and especially in subcapsular areas

Histologic grading of fatty change:

1+ = very small amounts mainly as droplets.
2+ = about one-quarter of lobule involved.
3+ = about half of lobule involved.
4+ = about three-quarters of lobule involved.
5+ = virtually entire lobule involved but not all liver cells with globules.
6+ = liver looks like adipose tissue; almost every cell with single large globule of fat.

Histological grading of hepatic fibrosis and cirrhosis:

1+ = present in scattered foci.
2+ = about one-quarter of lobules affected.
3+ = about half of lobules affected.
4+ = almost all lobes affected.

* PSL = around radicles of the hepatic veins, usually central or sublobular divisions.
‡ PP = periportal.

TABLE IV

Liver Pathology of Hypophysectomized-Thyroidectomized (HT) Dogs

Dog	Sex	Sacrificed: Time after hypophysectomy	Sacrificed: Time after thyroidectomy	Liver weight	Fatty acids in liver	Histological fat in liver	Hepatic fibrosis	Hepatic cirrhosis	Remarks
		days	*days*	*gm.*	*per cent*				
HT3	F	42	97	450	13.7	3-4+; mainly globules; PP*	0	0	0
HT6	M	181	135	390	3.9	0	0	0	PP polymorphs, round cells, and edema. Marked sinusoidal distention
HT8	F	446	419	989	16.2	6+; some lobes are almost fat-free	3+; mainly PSL*; some PP	+	Fibrosis greater than HT10 and less than HT22
HT10	F	447	398	1455	30.5	5-6+; PSL	2+; PSL	+	Fibrosis not quite as advanced as HT8 and more so than HT22
HT11	F	423	374	285	12.5	3+; patchy PSL	3+; PP	2+	Plasma cells PP; PP fibrosis not related to centrolobular fat
HT15	F	357	310	375	52.5	1-5+; very patchy even in same section	4+	3+; very mixed PP interstitial and PSL	Well advanced cirrhosis makes determination of pathogenesis almost impossible
HT18	M	296	250	405	32.5	5-6+; globules; fat-free patches	4+; PSL	3+; mainly PSL; some PP	Later stage than HT8 and HT10 with early fibrosis of portal tracts
HT21	F	262	217	398	14.3	3-4+; PSL	+; PSL	0	Pericentral fibrosis less advanced than HT10
HT22	F	356	311	412	11.2	5-6+; PSL. Lobes vary	4+; PSL	+	Fibrosis more advanced than HT8 but PP fibrosis not as marked as HT8 or HT18.

* Abbreviations as in Table III.

leucocyte infiltrations similar to those portrayed in Fig. 5 were observed around the sublobular veins.

Early Fibrous Tissue Reactions (*Precirrhosis*).—The uninterrupted series of changes detected in different livers revealed that the final cirrhosis commenced as the lesion described here as early fibrosis. Such early fibrotic reactions were identical in all the dogs, varying only in degree of severity. The initial changes are those portrayed in Figs. 3 and 5. It can be seen from these photomicrographs that in the regions of the central or sublobular veins the distance between the individual fat cells is distinctly increased. The tissue between the liver cells is faintly basophilic, this basophilia being due to an early thickening of the pericellular reticular fibers. These areas of thickened reticulum are clearly more highly cellular than is usual in such fatty areas, the increased cellularity being due to the presence of numbers of plasma cells, polymorphs, lymphocytes, and some fibroblasts (Fig. 3). For the most part, these inflammatory cells are distributed along the thickened reticulum, but numerous irregularly scattered foci of these same cells are also present. Large eosinophilic giant cells, usually with a single large contorted nucleus, are frequently scattered within, or in the neighborhood of, these cell foci (Fig. 5). The large number of these giant cells in the spleens of these animals (Fig. 6) suggests that these same cells may have infiltrated the liver by blood spread from the spleen. It must be added, too, that such foci of inflammatory cells are occasionally found scattered among those relatively fat-free liver cells towards the portal tracts. The most obvious site of infiltration of these inflammatory cells is around the walls of the central and sublobular branches of the hepatic veins, and it seems that these cells frequently occur here even when the reticular fibers around the fat cells are not yet obviously thickened (Fig. 5).

The thickening of the pericellular reticular fibers and the inflammatory cell infiltration are shortly succeeded by an accumulation of fibroblasts with long, vesicular, finely chromatic nuclei, and these cells, in turn, are followed by a further thickening of the reticulum, this time the result of collagen deposition. This combined series of reactions is regarded as early fibrosis of the centrolobular zones (Figs. 2 to 4).

With the progress of this early fibrotic lesion the reticulum thickens around the cells abutting on this primary zone of reaction, and subsequently the fibrosis becomes apparent even among the midzonal fat cells. The picture now seen reveals the presence of dense collagen with fewer fibroblasts but with new blood vessels in the central parts of the lobules. Radial extensions of these collagen fibers insinuate themselves among the fatty or non-fatty liver cells (Fig. 2). The centrolobular fibrous tissue of adjacent lobules now joins, forming a fibrous ring enclosing a centrally located portal tract and associated liver tissue of several lobules (Fig. 4).

With the contraction of this ring of fibrous tissue, the portal tracts are drawn nearer to one another and to the central zone of reaction, and some of the radiating fibrous tissue extends toward the centrally lying portal tracts

(Fig. 4). At this stage lobular distortion is initiated, and frank cirrhosis, which has obviously commenced around the central or sublobular veins, can be regarded as in progress.

Frank Cirrhosis.—As indicated in the introduction above, two pathologically distinct forms of cirrhosis were observed in the dogs which had both their thyroid and their pituitary glands resected. These two forms can be classified as (1) pericentral or perisublobular cirrhosis and (2) periportal cirrhosis.

1. Pericentral or Perisublobular Cirrhosis:—Both these terms are used here since the central vein may not be easily detectable, but instead a larger radicle of the hepatic vein forms the focus around which occurs the early fibrosis described above. The important point to be made is that *this is a cirrhosis commencing around the radicles of the hepatic rather than around the portal veins.*

With the progress of the early fibrosis described above, dense collagen masses form in the center of the lobule, the portal tracts are drawn closer, and are usually passively submerged in the progressing fibrosis (Fig. 7). At this stage the hepatic radicles draining the subcapsular lobules are obviously fibrotic, and the capsule itself is drawn in so that the liver surface has a dented appearance. Such pictures are indistinguishable from those described by Ashburn, Endicott, Daft, and Lillie (6) in the later stages of the cirrhosis produced in rats by diet and toxins. These workers demonstrated conclusively by injection of a carbon mass, that the affected veins were *hepatic* radicles.

At this stage reticular thickening followed by fibrosis commences in the *midzones* of the lobules and replaces the remaining liver cells. Such midzonal or intralobular fibrosis (Fig. 7) hastens the obliteration of those liver cells which are enclosed by the fibrous ring formed by the joining-up of the fibrosing hepatic radicles of neighboring lobules (Figs. 4 and 14). Even in the late stages of this form of cirrhosis, concentric fibrosis around the portal tracts is unusual (compare Fig. 4 with Figs. 9 and 10, and Fig. 13 with Fig. 14).

In the final stages of the centrolobular cirrhosis complete lobules are replaced by dense, fibrous scar tissue containing several portal tracts with their small atrophying bile ducts and several newly developed vessels (Fig. 8). Ultimately the hepatic architecture is so grossly distorted and the fibrosis is so diffuse that it becomes impossible to determine the site of origin of the fibrosis. However, in the livers obtained from the dogs in this experiment all stages of the reaction were detected. Even in the same lobe of one liver or in different lobes of the same liver, considerable variations were seen in the stages of evolution of the cirrhosis.

One of the striking features of the severely cirrhotic livers in this study was the complete absence of nodular hyperplasia and the rarity of bile duct proliferation.

2. Periportal Cirrhosis:—Since the fibrosis, in the two livers showing this lesion, clearly commenced in and around the portal tracts, this classification seems justified (see Figs. 9 to 13).

The initial reaction, detected around the smallest discernible portal radicles, is an accumulation of plasma cells and lymphocytes with an occasional polymorph around the tiny bile ducts (Fig. 12). This periductal cellularity, together with some thickening and edema of the periportal connective tissue, throws the affected tiny ducts, usually difficult of detection, into prominence (Figs. 9 and 10). In many instances the bile ducts themselves appear to be obliterated completely. Should they survive, the small portal tracts are made even more prominent (especially in preparations for reticulum or those stained with Mallory's connective tissue stain); this greater prominence is now due to the fibroblasts and collagen fibers being deposited concentrically around the portal tracts (Figs. 10 to 12). At this stage the liver, when stained with hematoxylin and eosin (Fig. 9), assumes an appearance similar to that portrayed by Watson and Hoffbauer (7) (*cf.* their Fig. IIB with our Figs. 9 and 10) and described by them as early cholangiolitic cirrhosis.

Progress of this periportal lesion is manifest by the extension of the fibrous tissue radially from the portal tracts into the lobules abutting on the affected portal tracts (Fig. 11). These tracts are now drawn closer to one another and to the radicles of the hepatic veins; intralobular fibrosis also occurs, and, as in the perihepatic vein cirrhosis described above, the lobules are eventually obliterated completely by dense scar tissue (Fig. 13).

Where extensive areas of liver are replaced by frank fibrous tissue, it is obviously impossible to determine the pathogenesis of the cirrhosis. However, the virtually complete absence in these dogs of nodular hyperplasia (usually encountered in severely cirrhosed livers) made the interpretation of the course of the lesions in our dogs very easy. Moreover, the graded series of reactions encountered in this experiment, in different animals and in different lobes of the same liver, left little doubt as to the pathogenesis of these two different forms of cirrhosis.

DISCUSSION

Our observations confirm for the dog the findings of Lillie *et al.* (4) and of Ashburn *et al.* (6) in the rat, that experimentally induced cirrhosis superimposed on a fatty liver usually commences and proceeds primarily around the radicles of the hepatic rather than of the portal veins.

In the dogs reported on here, this centrolobular cirrhosis occurred in animals with fatty livers. This finding would seem to add support to the contention that one of the important factors operating in the production of hepatic cirrhosis is a long standing fatty change. As early as 1938 Connor (8) stated, "There seems no room to doubt that long-standing fatty infiltration of the liver is a mechanical factor of great importance for the development of fibrous tissue. . . ." Recently Glynn (9) and Handler and Dubin (10) have supported Connor's view. This opinion is based on the fact that, no matter how the fatty liver is induced, whether by malnutrition, by toxins of chemical or bac-

terial nature (11–13), or by experimental pancreatectomy (14), cirrhosis is a frequent sequel.

From Tables III and IV it is clear that hepatic fibrosis of varying severity was detected in the livers of 4 thyroidectomized dogs and in 7 of the animals with the two operations (HT). In the latter group, frank cirrhosis of varying severity was diagnosed in 6 animals, while in only one of the thyroidectomized dogs (T19, Table III) was the fibrotic reaction sufficient to result in the lobular distortion which we have taken as an essential requisite for the distinction between hepatic fibrosis and frank cirrhosis. Comparison of Tables I and II reveals, furthermore, that in none of the thyroidectomized dogs was the fatty acid content of the liver greater than 22.7 per cent, whereas in several of the hypophysectomized and thyroidectomized dogs (HT) the fatty acid content of the livers was above 30 per cent and in one (HT15) it was 52.5 per cent. From a study of the chemically determined degree of fatty change, it is clear that, even among the HT dogs, no correlation can be established between the extent and severity of the hepatic fibrosis and the amount of fatty acid in the liver (Table IV).

It would seem from the findings in HT15 and HT18 (Table IV) that severe fatty change was associated with the most advanced cirrhosis. However, HT10, with a fatty liver of equal severity to that in HT18, had a much milder fibrosis and lobular distortion than the latter. These findings, together with the fact that HT22 (Table IV) with much less fat than either of those animals, had a fibrosis and cirrhosis more marked than did HT10 and almost as severe as in HT18, negate any attempt at correlation between severity of the fatty change and the onset and development of hepatic fibrosis.

Further, comparison of dog T12 (Table III) with dogs HT8, HT11, and HT22 (Table IV) or of dogs T12 and T14 (Table III) with dog T19 (Table III) makes even clearer our inability to predict, on the basis of the degree of fatty change, whether fibrosis or cirrhosis could be anticipated in histological sections of any liver.

Other evidence in support of the view that the fatty change is not alone responsible for stimulating fibrous tissue reactions in the liver is forthcoming from another study. As will be shown there, even the centrolobular cirrhosis described here has been observed in non-fatty livers (15). Moreover, of the two pathogenetically distinct forms of hepatic cirrhosis encountered in HT dogs, the centrolobular cirrhosis clearly occurred within the fatty liver lobules whereas the periportal fibrosis, observed in the livers of two animals, bore no detectable relation to the presence or absence or to the location of the fatty change. Thus in dog HT11 (Table IV) the fat content of the liver was relatively low, as judged by chemical and histological procedures, and the fibrotic reaction occurred in the non-fatty zones of the liver lobules (see Figs. 9 to 12.)

Whatever the final explanation of the lack of consistent correlation between

the fatty change in the liver and the onset of fibrosis in our dogs, we wish to suggest that the presence of long standing fatty change is not alone responsible for the onset of cirrhosis. The most that can be said at this stage is that severe fatty change around the central veins may facilitate the evocation of centrolobular cirrhosis.

Several other interesting facts emerge from the data accumulated in this study. Firstly, two pathogenetically distinct forms of fibrosis were detected in the dogs with both operations, even though they were subjected to the same experimental procedures. This rather unexpected finding indicates that the factors determining the localization of fibrous tissue reactions in the liver are still quite obscure.

Secondly, the incidence of severe fibrosis (amounting to cirrhosis) was far more frequent among the dogs with the two operations than among the animals deprived only of the thyroid. HT3 and HT6 (Table IV) were the only dogs with the two operations that did not develop hepatic fibrosis. This can probably be ascribed to the short time which had elapsed between the removal of the second gland (thyroid) and examination of the liver.

The removal of the hypophysis[2] would seem to have hastened the onset and rate of progress of fibrosis in the livers of our hypophysectomized-thyroidectomized dogs. Thus, severe fibrosis could be detected as soon as 250 days after the second operation in one dog (HT18, Table II), whereas in animals from which the thyroid alone was removed similar degrees of fibrosis were not present even after 300 days. Furthermore, the most severe fibrosis among the thyroidectomized dogs occurred in T19 (Table I) 300 days after removal of the thyroid, whereas a more severe and more extensive fibrosis was encountered within 250 to 300 days after thyroidectomy in dogs from which the pituitary had been previously removed.

The above considerations suggest that the presence of the pituitary in some manner inhibits cirrhosis-inducing factors from operating in the thyroidectomized dog.

Another fact emerging from this investigation is that both types of cirrhosis described here, which have usually been attributed solely to exogenous causes,

[2] Fibrous tissue proliferation has been shown to occur in the livers of hypophysectomized dogs by Graef *et al.* (16) and by Chaikoff *et al.* (17). The findings of the latter investigators differ somewhat from those of Graef *et al.* in that the development of the fibrous tissue was not preceded by an increase in the fat content of the liver. Graef *et al.* concluded that hypophysectomy had little if anything to do with the hepatic lesions and that the hypothalamic lesions seemed to have a pivotal rôle in the hepatic changes. Careful histological studies of the hypothalamic regions in our own hypophysectomized animals (17) by serial-section failed to reveal any evidence of damage to this important center. This fact, together with the absence of fat from the livers of our hypophysectomized dogs (17), indicates that the pathogenesis and possibly the etiology of the hepatic fibrosis in our hypophysectomized animals differed somewhat from those described by Graef *et al.*

can be induced by metabolic disturbances following surgically imposed endocrine deficiency. This evidence indicates that the endocrine disturbances known to occur in association with liver disease and chronic malnutrition deserve more attention than they have previously received in studies directed at the elucidation of the mechanisms involved in the production of hepatic cirrhosis.

SUMMARY

1. The reactions of the dog's liver to (*a*) thyroidectomy and (*b*) both hypophysectomy and thyroidectomy are described.

2. Fatty changes of varying severity were detected in 8 of the 9 hypophysectomized-thyroidectomized dogs, hepatic fibrosis in 7, and severe cirrhosis in 4 animals of this group.

Among the thyroidectomized animals histologically demonstrable fatty livers were present in all 8, mild fibrosis was observed in 4, while early and mild cirrhosis was diagnosed in only one dog.

3. Two pathogenetically distinct forms of cirrhosis were present in the livers of dogs with the two operations, namely (*a*) cirrhosis initiated and developing around the radicles of the hepatic veins, and (*b*) periportal cirrhosis.

Both forms of cirrhosis occurred in dogs that were subjected to the same experimental procedures, and both forms could be found in the same liver.

The pathogenesis of these two forms of cirrhosis is described.

4. The relation between fatty change in the liver and the genesis of fibrosis is discussed, and it is suggested that, while fatty change may facilitate the evocation of cirrhosis, this reaction on the part of the supporting and vascular elements of the liver is not solely dependent on the fatty change in the liver cells.

5. The relation between the endocrines and hepatic cirrhosis is discussed. Since cirrhosis was slight in the fatty livers of thyroidectomized dogs, whereas it was often advanced in hypophysectomized-thyroidectomized dogs, it is suggested that in the absence of the pituitary cirrhogenic mechanisms are facilitated in the dog.

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EXPLANATION OF PLATES

PLATE 1

FIG. 1. Section of liver of dog HT21 deprived of both pituitary and thyroid glands for 217 days. Note small portal tract in center surrounded by virtually fat-free liver cells. The three radicles of the hepatic veins are surrounded by very fatty liver cells indicating the centrolobular location of the fatty change. Note also some edema and cellular infiltration around the hepatic radicles. Hematoxylin and eosin. × 47.

FIG. 2. Section of liver of dog HT10 deprived of both pituitary and thyroid glands for 398 days. Depicting early fibrotic changes (precirrhosis) among fatty cells in centrolobular area. Note that the small centrally located portal tract does not show any thickening or cellular infiltration. Hematoxylin and eosin. × 47.

FIG. 3. Section of liver of dog HT10. Showing towards top and at left initial changes heralding precirrhosis in the centrolobular fat. The inter- and pericellular reticular fibers are thickened. There is an infiltration of round cells, polymorphs, and a few fibroblasts around and near the longitudinally sectioned hepatic radicle at left. The small portal tract at the bottom right of the picture shows no signs of fibrosis. Hematoxylin and eosin. × 98.

FIG. 4. Section of liver of dog HT10. In this section the centrolobular fibrosis has progressed beyond that shown in Fig. 2. Collagen fibers have now been laid down in the region of the initial reaction within the centrolobular fat. In addition the fibrosis around the individual central or sublobular vessels is now becoming linked with that in the neighboring lobules (early cirrhosis). There is at this stage some early fibrotic reaction around the portal tract lying in the center of the area delineated by the linking of the perihepatic fibrous tissue bands. Hematoxylin and eosin. × 54.

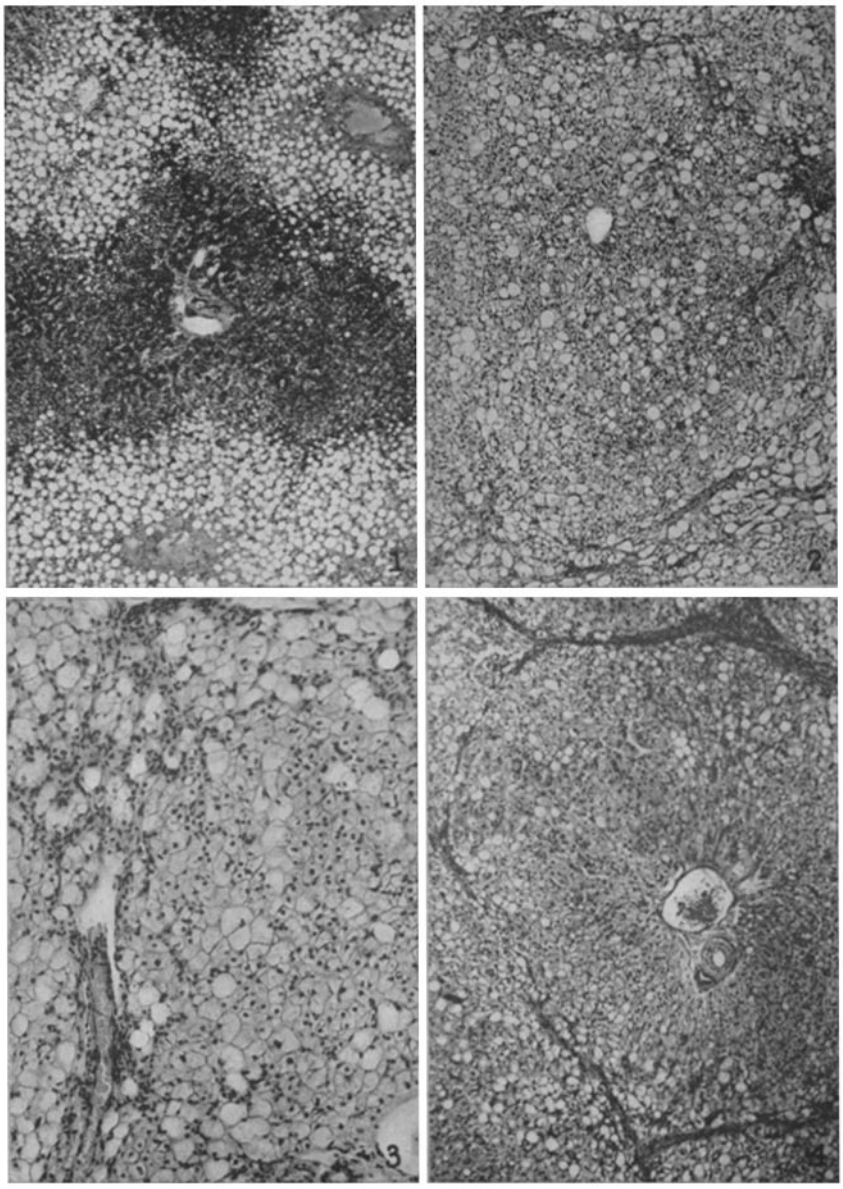

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PLATE 2

FIG. 5. Section of liver of dog HT10. High power view of early reaction near central vein to show round cell and polymorph infiltration preceding early fibrosis. Large giant cells such as that seen toward the top right corner of this picture are commonly encountered in these early reactions. Hematoxylin and eosin. × 190.

FIG. 6. Section of spleen of dog HT10. The large numbers of giant cells in the spleen of this animal, whose liver is portrayed in Fig. 5, and the fact that the splenic giant cells are morphologically identical with those in the liver suggest that the hepatic giant cells may have originated in the spleen. There is only one contorted nucleus in these giant cells. Hematoxylin and eosin. × 140.

FIG. 7. Section of liver of dog HT18 deprived of both pituitary and thyroid glands for 250 days. A later stage in the progress of the centrolobular or perihepatic vein fibrosis. The early fibrosis depicted in Figs. 2 and 4 has progressed to dense, well marked fibrosis with lobular distortion (cirrhosis). Early fibrosis has begun above and to the right of the almost centrally located portal tract. This latter intralobular fibrosis begins within the lobule around the fatty liver cells in the same manner as depicted in the centrolobular region in the figures above. Hematoxylin and eosin. × 75.

FIG. 8. Section of liver of dog HT18. Stage subsequent to that depicted in Fig. 7, showing terminal obliteration by fibrous tissue of an area (as shown in Fig. 4) delineated by the early linking of perisublobular fibrosis. Hematoxylin and eosin. × 47.

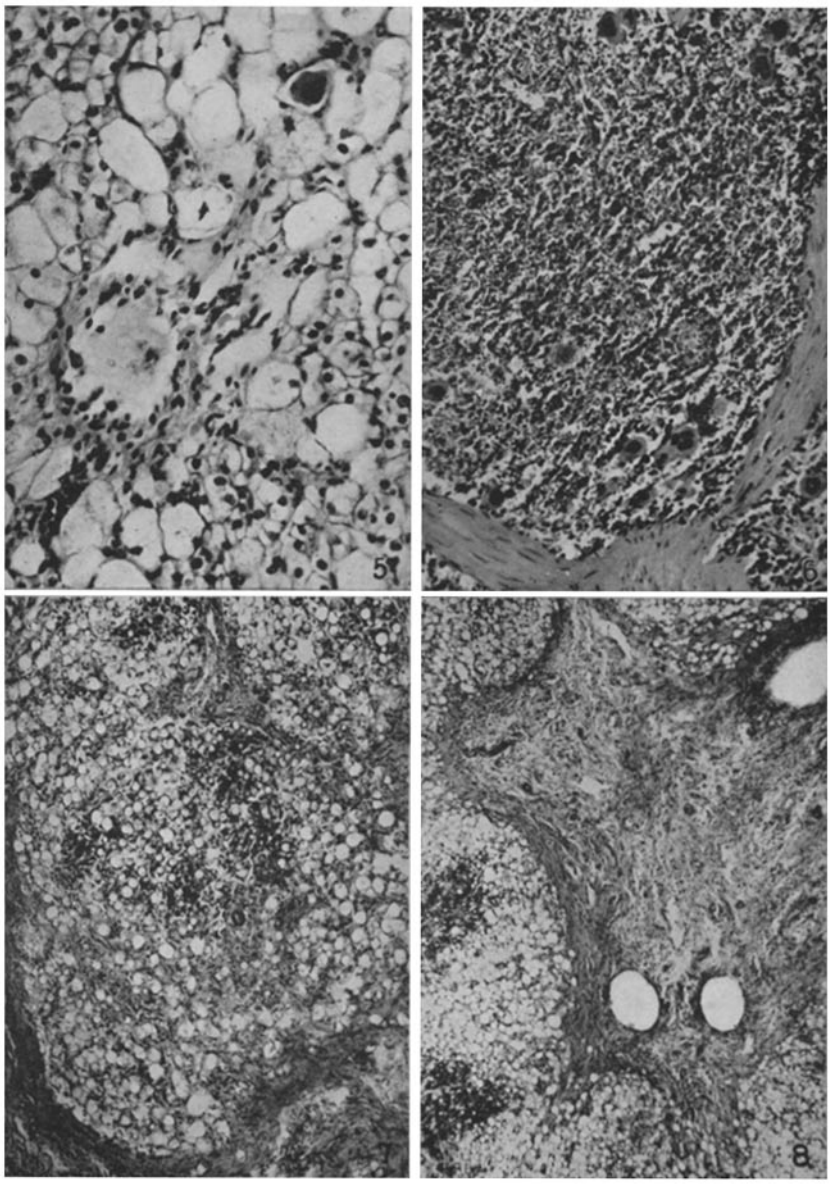

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PLATE 3

FIG. 9. Section of liver of dog HT11 deprived of both pituitary and thyroid glands for 374 days. The small and medium sized portal tracts have become prominent by virtue of the periportal cellular infiltration and thickening. Note that this early periportal reaction is occurring despite the virtual freedom from fat of these portal tracts. This is regarded as an early stage in the pathogenesis of portal cirrhosis. The initial lesion here is clearly periportal. Hematoxylin and eosin. × 83.

FIG. 10. Section of liver of dog HT11. Demonstrating the increase in collagen fibers around the small portal tracts of the liver depicted in Fig. 9. Mallory's connective tissue stain on another section from the same liver as that depicted in Fig. 9. × 41.

FIG. 11. Section of liver of dog HT11. Later stage in the pathogenesis of periportal cirrhosis showing increased fibrosis around portal tracts with early extension of fibrous tissue among the liver cells abutting on the affected portal tracts. This is another lobe of the liver depicted in Figs. 9 and 10. Mallory's connective tissue stain. × 75.

FIG. 12. Section of liver of dog HT11. The concentration of plasma cells and polymorphs around the bile duct rather than around the hepatic artery or portal vein in this small portal tract is clearly shown. From same liver as depicted in Figs. 9 to 11. Hematoxylin and eosin. × 330.

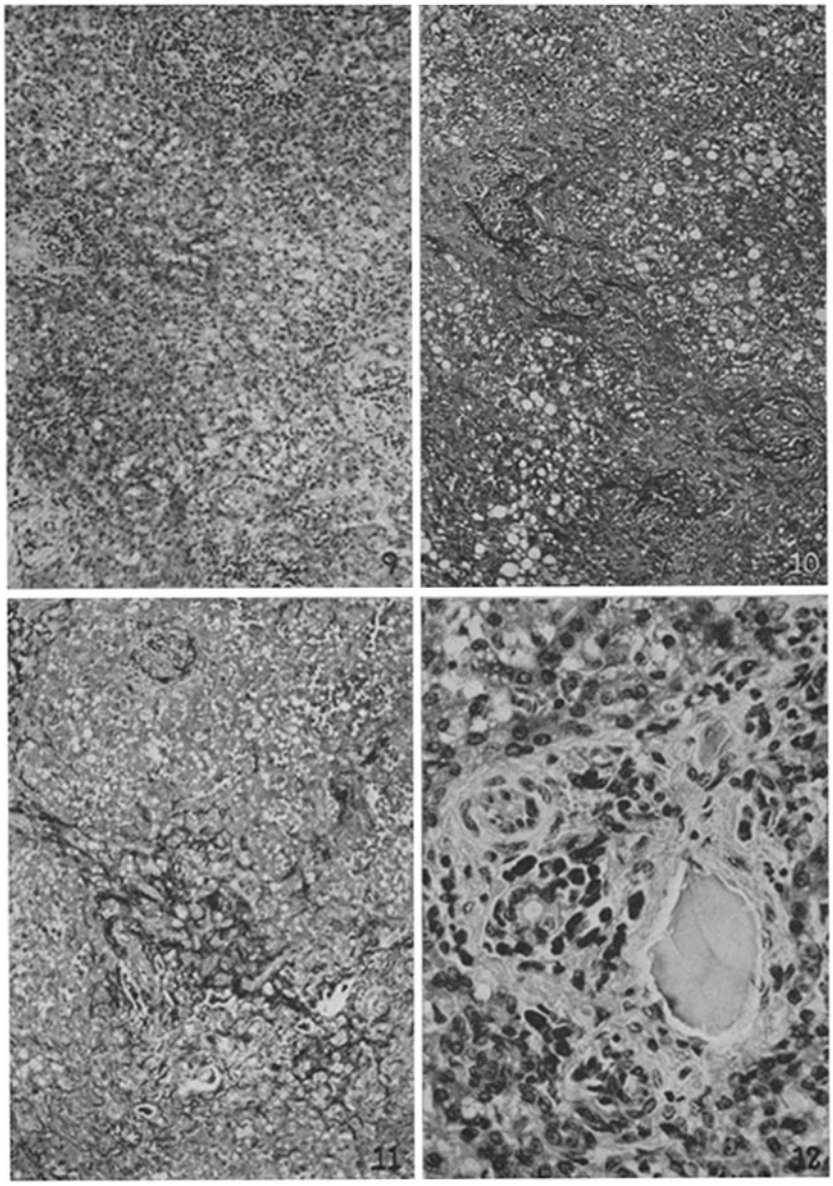

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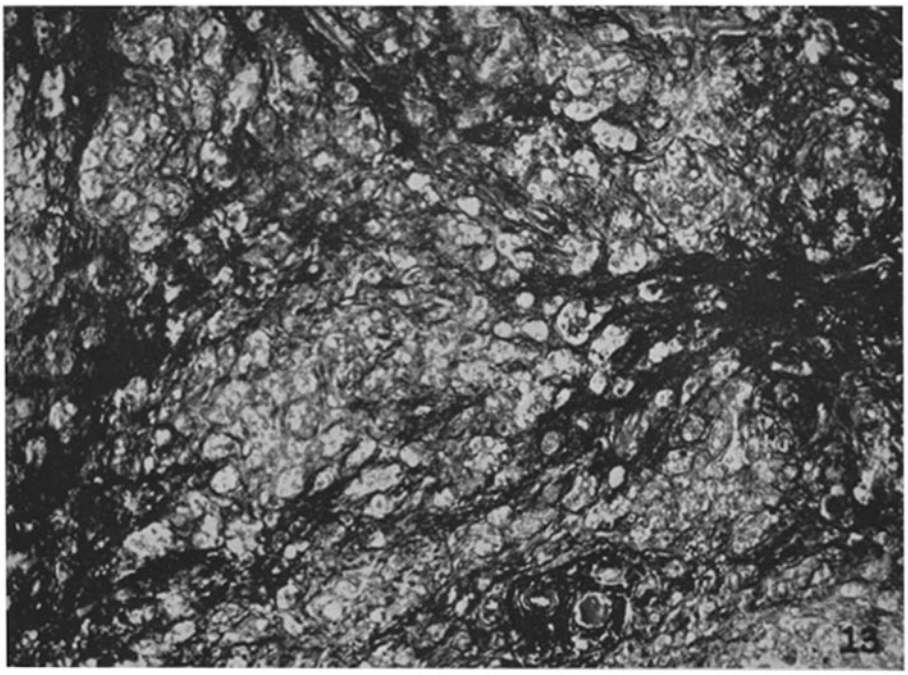
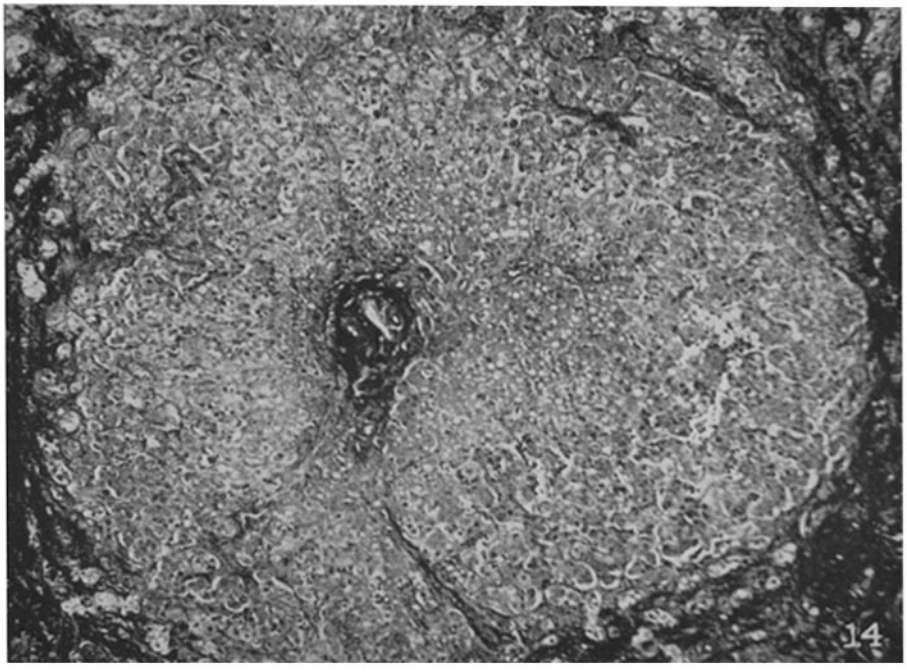
PLATE 4

FIG. 13. Section of liver of dog HT11. Another lobe of same liver as that depicted in Figs. 9 to 12, showing here a later stage in periportal cirrhosis with severe involvement of parenchyma by the fibrous tissue extending from the densely fibrotic portal tracts seen on both the right and the left of the picture. Note, at bottom center, the dense concentric fibrosis around the small portal tract (a prominent finding in this type of cirrhosis) and compare with the relatively unaffected portal tracts, of similar size, in livers with the perihepatic radicle fibrosis in Figs. 2, 4, 7, and 14. Mallory's connective tissue stain. × 140.

FIG. 14. Section of liver of dog HT15 deprived of both pituitary and thyroid glands for 310 days. Late stage in perihepatic radicle fibrosis showing dense fibrosis in laterally located hepatic radicles with extension of fibrosis into the parenchyma enclosed within fibrous "ring" (see fig. 4). Note that the centrally located portal tract shows relatively little reaction or thickening in this liver as compared with the periportal changes depicted in Figs. 9 to 13. Mallory's connective tissue stain. × 125.





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