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Histopathology of the adrenal cortex in diabetic capillary disease

Robert P. Gentry
University of Nebraska Medical Center

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THE HISTOPATHOLOGY OF THE ADRENAL CORTEX

IN DIABETIC CAPILLARY DISEASE

Robert P. Gentry

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THE HISTOPATHOLOGY OF THE ADRENAL CORTEX
IN DIABETIC CAPILLARY DISEASE

Diabetes mellitus, a disease in which the normal insulin metabolism of the body is disturbed, is among the most common of human diseases. There are probably over two million cases in the United States alone with an additional large potential reservoir of the disease (1). Now that insulin can control the hyperglycemia and coma of diabetes and the antimicrobial agents can decrease the danger of infections, the most important problem in clinical diabetes today is probably that of vascula disease (2). These vascular changes may involve the medium-sized arteries of the myocardium, lower limbs, and brain; the arterioles, especially of the kidney; and the capillaries of the renal glomeruli and the retinae. It is these latter conditions, diabetic retinopathy and intercapillary glomerulosclerosis, which are receiving an increasing amount of attention from investigators. These lesions are apparently increasing in frequency and are becoming an ever increasing factor in the morbidity and mortality of diabetic patients (3-7). Physicians are therefore obligated to try to find the basic cause or causes of these complications so that they might be prevented or at least controlled.

DIABETIC RETINOPATHY.

The exact nature of diabetic retinopathy was poorly understood until Ballantyne and Loewenstein (8) described the condition in great

detail in 1943 using special stains on flat preparations of whole
retinae. Since then diabetic retinopathy has emerged as a distinct
pathologic entity, and there is rather good agreement among various
workers as to the basic pathology involved (5, 9-13). The original
defect is now known to e the development of numerous discrete sac-
cular aneurysmal dilata ions 30 to 90 micra in diameter arising from
the venous side of the apillary bed in the inner nuclear layer of the
retina. The larger micro-aneurysms can be seen through the ophthal-
moscope as small red spots resembling deep hemorrhages. However the
hemorrhages, which may also be present, tend to be larger, have less
distinct outlines, and are more transient. The aneurysms are usually
thin-walled but may have markedly thickened walls containing a muco-
polysaccharide material. Often the only findings in the eye are the
aneurysms in the posterior pole of the eye, but as the process prog-
resses, hard white or yellowish exudates with distinct borders begin
to appear. These tend to coalesce into larger masses causing visual
disturbances, especially as the macular region is involved. Since
these exudates and hemorrhages are often found near the aneurysms, it
is thought that there may be a weakening of the capillary wall at
that particular point. As the retinopathy becomes more advanced
there may be distortion of the capillary and venous pattern with neo-
vascularization which eventually may lead to the more serious retinitis
proliferans and retinal detachment.

It is generally considered that this aneurysmal lesion is quite
specific for diabetes mellitus. Capillary aneurysms of the retina

are found in other disease processes and even in normal retinae (14-16), but they are much fewer in number, tend to be more fusiform in appearance, involve the arterial side of the capillary, and are found in damaged areas or at he periphery of the retina. Friedenwald (17) feels that diabetic retinopathy is a primary vascular disease while in other diseases the aneurysms are a response to local tissue injury. Although many diabetics also have hypertension with associated hypertensive retinopathy, it has been shown that diabetic retinopathy is independent of hypertension, arteriosclerosis, or atherosclerosis since the typical aneurysms are found in many cases in the absence of these other conditions.

Attempts have been made to find similar capillary aneurysms in other body tissue, but the only other lesion which occurs to any degree in diabetics is intercapillary glomerulosclerosis. These two capillary complications have many similarities histologically, histochemically, and clinically. Both have dilated capillaries with associated thickened walls which stain similarly as mucopolysaccharides (18, 19), and clinically they are often found together. Although some patients with retinopathy show no glomerular lesions, almost all—if not all—patients with demonstrable kidney lesions have macroscopic or microscopic retinal lesions. Careful microscopic studies of whole retinae have shown that all cases of glomerulosclerosis studied also had retinopathy (5, 9). Because of this close similarity the two conditions are generally considered to be the same pathologic process modified by their occurrence in different anatomical structures.

INTERCAPILLARY GLOMERULOSCLEROSIS.

The capillary changes of the kidney have been the subject of much discussion and stud since the original description by Kimmelstiel and Wilson of the so-called intercapillary glomerulosclerosis (20). There is more disagreemdnt as to the nature of this lesion than is the case of the retinal lesion. Two types of lesions are described at the present time (3, 21-25). The typical nodular lesion as originally described by Kimmelstiel and Wilson is characterized by rounded, focal collections of hyaline-like material located in the center of a glomerular lobule. These masses which vary in size from 20 to 120 micra usually have associated dilated and congested capillaries which tend to encircle them. The h line-like material stains as a mucopolysaccharide and shows typic ly arranged laminated bands of fibers when stained with silver stains (19, 22). Many authors believe that this nodular form is just the end stage of a diffuse form of hyalinization of the glomerular capillaries. This diffuse form of the disease is more difficult to evaluate since similar changes may be found in glomerulonephritis and in arteriolonephrosclerosis. However some authors state that the diabetic form may be differentiated by the hyalinization of the afferent and efferent arterioles, the characteristic laminated bands as shown with silver stains, and the increased amount of lipoid material within the capi laries (22, 24, 26). The differences in criteria for describing this lesion probably leads to the rather wide variation in reported incidence of intercapillary glomerulosclerosis in diabetic patients (22-25).

Although many pat'ents with typical glomerular lesions demonstrated at autopsy have no clinical symptoms of kidney disease, the characteristic syndrome is the appearance of albuminuria, edema, and hypertension in patients with diabetes of long duration (24). The course of the syndrome is relatively slow, and the patient may live months to years after the syndrome is first recognized. Azotemia with eventual renal failure is the usual cause of death in the young diabetic, but the older patient is just as likely to die from cardio-vascular complications (3). Since this process can only be diagnosed definitely by microscopic examination of the kidneys, it is difficult to follow the course of the disease in living patients. Therefore the closely associated retinal lesions may be a valuable guide in following the more serious kidney disease.

ETIOLOGY OF THE CAPILLARY LESIONS.

Many theories as to the cause of the vascular lesions in dia-betics have been proposed, but as yet none has been definitely proven. The capillary lesions ar apparently fairly specific to the diabetic patient, yet something else must be involved since not all diabetics develop them. Zubrod (27, 28) suggests that patients with capillary complications probably do not have a simple insulin deficiency diabetes since his patients with these lesions rarely had previous episodes of acidosis even without the use of insulin. He states that a relative excess of the hyperglycemia-glycogenolytic hormone from the islets could explain this phenomenon. However White (29) reports that a high percentage of her young diabetics do have rather frequent

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episodes of acidosis. Heredity has been suggested as a possible factor, especially sinc diabetics with capillary lesions tend to have increased capillary fragility (30-34). However is such a de-ficient vascular system caused by a hereditary disturbance or some other factor related to the diabetic process? More women tend to have these complications (35, ;6), therefore sex may be a factor, but the finding of the disease in both sexes does not substantiate this.

At the present time the duration of the diabetic process stands out as one of the most important factors involved in the development of the complication since most of the patients with capillary dis-ease have had diabetes longer than 10 years (24, 37-39). However long duration of diabetds does not necessarily mean there is no hope for that particular patient. Bell (24) reported 28 of 93 patients who had diabetes longer than 20 years had no serious vascular disease, an White (29) states that 8% of her young diabetic patients aving the disease longer than 5 years showed no evidence of any vascular disease. The severity of diabetes as based upon the need for taking insulin and not upon the insulin dosage has been suggested as a possible factor especially in the younger diabetic. He usually has a more severe diabetes and usually has more severe complications than does the older diabetic. Yet many patients with very mild diabetes may suffer from severe capillary lesions while more severe diabetics may escape the disease (2). The degree of control of the diabetic patients has become one of the biggest arguing points as to

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the cause of these vascular complications. Some investigators have

shown that there is apparently very little correlation between the

lesions and the control if diabetes (40, 41). Yet others show that

good control markedly decreases the incidence of the process (42-47).

It is possible that control will not prevent the appearance of the

process, but it may minimize the progression of the disease (35).

The concept of humoral factors has recently been supported by

the finding of no glomerulosclerosis in one kidney of a diabetic who

showed marked capillary disease in the other kidney. The one kidney

without capillary lesions had a thrombus in the renal artery with

resultant decreased circulation to that particular kidney (48). Since

the lesions have increased mucopolysaccharide deposited in

the walls of the vessels there may be a relationship between pro-

longed hyperglycemia or increase in serum polysaccharides and the

deposition of material in these vessel walls (49-51). Although

lipemia is usually connected with atherosclerosis, there may also be

an associated factor in he capillary disease of diabetes. Hartroft

(26) reports that fat emboli in the glomerular capillaries may cause

stasis in the vessels which eventually results in the thickening of

the basement membrane and finally lesions resembling those of

inter-capillary glomerulosclerosis.

ADRENAL CORTICAL HORMONES. In recent years Becker (11, 52)has

proposed a theory that the adrenal cortex is involved in this disease

process. Variou investigators have accumulated considerable

evidence supporting this theory, but much of it is still rather in-

direct evidence. Various observations indicate that excessive adrenal cortical activity may be related to the onset and progression of diabetic capillary lesions. Diabetic retinopathy has been shown to appear for the first time or increase in severity in diabetics who are pregnant (11, 53). Some of these women also showed some regression of the micro-aneurysms following delivery. These changes may be caused by the increased adrenal cortical activity during pregnancy, but there are also other metabolic and endocrine changes in the pregnant woman. Retinal and glomerular lesions similar to those in diabetics have been described in nondiabetic patients following treatment with corticotropin (54, 55). The retinal lesions of these patients were found to disappear following cessation of the therapy. Diabetics under good control and with no known complications tend to run normal or slightly lower than normal steroid levels in their urine (56-60). However most diabetics in acidosis, with associated hypertension, or with retinopathy tend to excrete excessive amounts of free oxysteroids in their urine (60-62). It has also been shown that many diabetics fail to show the normal eosinopenia of at least 50% following the injection of corticotropin but do have a normal response to cortisone (11, 63). These patients were invariably free from any demonstrable capillary lesions. Becker (52) has demonstrated that most patients with retinopathy show a prompt response to the corticotropin injection. All of these clinical findings tend to suggest that patients with capillary lesions have increased activity of the adrenal cortex as compared with patients without these lesions.

In recent years it has been found that decreased adrenal activity produced accidentally or therapeutically may improve the cap-illary disease. Poulsen (64) described the case of a diabetic woman who developed panhypopituitarism following pregnancy. Prior to preg-nancy she showed rather marked retinopathy, but following the hemor-rhagic destruction of her pituitary gland the eye lesions began to improve until no visible evidence of disease could be seen six years later. Recently hypophysectomy has been used on several diabetic patients with severe progressive vascular disease. The patients who survived the operation showed improvement in their vascular disease or at least no progressi n of the process (65, 66). Adrenalectomy in similar patients has also shown rather favorable results as far as the capillary disease is concerned (67-70). Testosterone has been used in some patients with favorable results (71, 72). Since it can cause marked atrophy of the hypophysis with marked lipoid depletion and atrophy of the zona fasciculata of the adrenal in rats, it is conceivable that the improvement may be caused by inhibition of the adrenal cortical hormone (73, 74).

Increased adrenal cortical activity has also been shown to cause experimental lesions in animals. Lukens and Dohan (75) showed that a dog made diabetic by injection of anterior pituitary hormone had lesions in its kidneys similar to those found in intercapillary glomerulosclerosis. Ric (76) and Bloodworth (77) have produced nodular glomerular lesions in rabbits by daily injections of cortisone but none with corticotropin injections. Becker (11) showed that renal

lesions could be produced in 30% of nondiabetic rabbits and 75% of

alloxan-diabetic rabbits by cortisone injections. A few of the dia-

betic rabbits also showed what appeared to be retinal aneurysms. Alloxan

diabetes alone failed to produce the glomerular lesions.

Other studies have shown that rabbits made diabetic by alloxan tend to

excrete less steroids in their urine (78). Becker (52) is now

working on experimental animals to find if nutritional or enzymatic

deficiencies of the adrenal cortex might be a cause of the metabolic

disorder involving the capillaries.

The phase of study with which this paper is most concerned is the

finding of histological differences in the adrenals of diabetics with

capillary disease and those without capillary disease. Becker

(11, 52) reports that the adrenal glands from 22 patients with inter-

capillary glomerulosclerosis were 24% heavier than those from 23

patients free from the disease. He also found that microscopic sec-

tions of adrenal glands showed differences in the degree of lipoid

vacuolization in the zona fasciculata. Eighty-six per cent of the

adrenals from 64 patients with diabetic nephropathy showed increased

vacuolization while only 12% of those from 91 patients without any

diabetic renal disease showed increased vacuolization. The adrenals

from 75% of 91 nondiabetic controls also showed this increased amount of

lipoid deposits. This difference in vacuolization in any of the groups

could not be explained on the basis of the cause of death alone.

Patients were divided into three groups depending on the cause of death:

(1) severe burns, traumatic shock or hemorrhage, or severe

infection, (2) chronic d bilitat ng disease, carcinoma, or chronic
infection, and (3) cardiorenal disorders or sudden accidents.
Pa-tients with intercapillary glom rulosclerosis and patients
without diabetes still showed a uch higher incidence of increased
lipoid vacuolization of the adrenals as compared with the diabetics

with-out glomerulosclerosins in all three categories. The
nondiabetic controls did show less vicuolization than did the
patients with diabetic nephropathy in group 1. Uremia or acidosis in
these patients did not seem to a ter the percentages to any
significant degree either. These findings tend to indicate that
there is a difference in the secretpry activity of the zona
fasciculata in diabetics with glomerulo clerosis as compared to those
without any glomerulosclerosis, and the activity of the former is
similar to that of nondiabetic patients. Becker (52) and Russi (79)
also report an increased incida ce of adenomas of the adrenal cortex
among diabetics and especially in those with renal lesions.

Such findings point strongly to the adrenals as active com-ponents
in the development of capillary complications in diabetics. However is
this increased adrenal cortical activity a cause of the lesions or
merely an accompanying factor?   If this hypothesis is true, then
patients witl acromegaly or cushing's syndrome should show an
increased incidence of capillary disease, but in a small number of
cases studied Ricketts (39) has not found such to be true. Among 16
patients with cromegaly and 10 patients with Cushing's syndrome 10
of them showed evidence of diabetes, and only two showed .

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true diabetic retinopathy. Much study is still needed on this sub-
ject before any definite conclusions can be made. It is the purpose of
this paper to further study the histopathology of the adrenal glands
among diabetics and nondiabetics to see if the findings of Becker can
be substantiated.

CASE MATERIAL.

All diabetic patients coming to autopsy during the past ten
years at University Hospital were used in this study. This included
40 patients of both sexes and of various age groups. Since most of
these patients died from cardiovascular and/or renal disease, 20
nondiabetic patients with similar conditions were picked at random
from the autopsy files as controls. In this manner it was hoped that
relative changes in the adrenal cortices might be shown in the various
complications of diabetes--especially the retinal and renal capillary
diseases.

The case records or each patient were studied to correlate the
clinical findings with the pathological findings at autopsy. Special
attention was paid to th duration of diabetes, the blood pressure, the
ophthalmoscopic studies, the nonprotein nitrogen levels, and the cause
of death. The kidneys of each patient were studied microscopi-
cally to determine the nature of any kidney pathology which might be
present. Particular care was taken in determining whether the diabetic
kidneys had intercapillary glomerulosclerosis or not. The nodular and
diffuse lesions classified as glomerulosclerosis are shown in figures 1
and 2. These studies were made on sections stained with Hematoxylin

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and Eosin stains with a few sections stained for connective tissue or
fat droplets. Microscopic sections of the adrenal glands were then
studied without knowing the nature of the disease process of the pa-
tient from whom they came. An attempt was made to determine the rela-
tive size of the cortex, but this was not possible because the glands
were not all cut at the same angle. The relative amounts of lipoid
deposits in the cortex and in particular the zona fasciculata were
classified I through IV. Grade I was defined as glands in which the
cells of the fasciculata contained practically no lipoid deposits
(Figure 3). As shown in the photomicrograph the cells are small,
compact, and rather homogeneous in appearance. Glands defined as
grade II had spotty areas through the fasciculata which contained
vacuolated cells. The other cells appeared more like those in grade
I (Figure 4). Those classified as grade III showed diffuse lipoid
laden cells in the outer portions of the fasciculata. The inner zones
and the zona reticularis contained little or no lipoid material (Fig-
ure 5). The glands were classified as grade IV when the cortices
were practically a solid mass of lipoid-laden cells extending from
the capsule to the medulla (Figures 6 and 7). Again the sections were
stained with Hematoxylin and Eosin stains. As a result of this stain-
ing technique the lipoid material was dissolved from the cells leaving
the vacuolated space formerly occupied by the lipoid material. Sev-
eral sections stained with Sudan IV for fat showed similar patterns
to the other sections. The findings in the various diabetic and non-
diabetic patients may be found in Tables I and II.

TABLE I—DIABETIC PATIENTS

Pt.	Age	Sex	B.P.	Duration	Retinopathy	Nephropathy	Adrenals	NPN	Cause of Death
R.B.	19	F	140/80	4 yrs.	no	none	I	27	pneumonia
L.H.	22	M	218/140	14 yrs.	yes	diffuse	III	94	uremia
E.F.	27	F	240/140	14 yrs.	yes	diffuse	III	180	uremia
C.N.	28	M	134/88	19 yrs.	yes	diffuse	IV	82	uremia
H.M.	31	F	132/100	17 yrs.	yes	nodular	III	76	uremia
K.S.	32	M	90/60	14 yrs.	yes	diffuse	III	187	meningitis
R.P.	33	M	200/98	14 yrs.	yes	nodular	IV	165	uremia
W.S.	35	M	218/120	12 yrs.	yes	nodular	III	295	uremia
D.A.	37	M	174/104	27 yrs.	yes	nodular	III	114	uremia
H.C.	37	F	200/110	14 yrs.	yes	none	III	90	pyelonephritis
O.M.	38	F	220/120	18 yrs.	yes	diffuse	II	148	uremia
H.L.	42	F	120/80	6 yrs.	no	none	I	52	SBE
L.S.	44	M	118/86	15 yrs.	yes	nodular	II	44	gangrene-leg
R.D.	47	M	110/60	8 yrs.	?	none	IV	?	coronary
H.D.	50	F	115/75	20 yrs.	yes	none	I	25	pneumonia
E.E.	50	M	172/102	6 yrs.	no	none	II	275	CA of rectum
G.M.	51	F	98/64	12 yrs.	yes	none	I	?	coronary
S.P.	51	F	210/108	5 yrs.	?	nodular	IV	234	uremia
E.M.	53	F	198/122	5 yrs.	no	none	II	26	coronary
B.A.	54	F	160/90	11 yrs.	yes	diffuse	III	190	uremia

TABLE I—DIABETIC PATIENTS (cont.)

Pt.	Age	Sex	B.P.	Duration	Retinopathy	Nephropathy	Adrenals	NPN	Cause of Death
J.H.	54	M	102/72	23 yrs.	no	none	II	?	coronary
M.R.	57	M	100/54	6 yrs.	no	none	I	?	lung abscess
A.R.	57	F	210/90	10 yrs.	yes	nodular	IV	223	uremia
G.M.	58	M	132/84	10 yrs.	yes	nodular	II	82	coronary
G.S.	59	F	130/58	5 yrs.	no	none	I	?	hepatic cirrhosis
J.V.	61	M	134/88	9 yrs.	?	none	I	132	peritonitis
L.S.	64	F	210/140	8 yrs.	no	none	II	54	gangrene-leg
E.S.	64	M	150/76	6 mos.	no	none	I	101	CA of bladder
C.T.	65	M	162/88	5 yrs.	no	none	II	36	subdural hematoma
C.B.	65	M	150/70	25 yrs.	yes	none	II	31	CVA
J.S.	66	M	139/86	4 yrs.	yes	none	II	32	coronary
K.N.	70	F	178/84	1 mo.	no	none	I	?	CA of sigmoid
J. .	72	M	118/54	?	no	none	IV	?	gangrene-leg
L.W.	74	F	176/100	5 yrs.	no	none	III	54	CVA
W.G.	74	M	132/80	20 yrs.	yes	none	I	75	ASHD, cardiac failure
S.P.	75	M	150/80	4 mos.	no	none	II	34	coronary
D.P.	75	F	140/78	8 yrs.	no	none	II	?	ASHD
W.L.	76	M	90/60	18 mos.	no	none	II	108	coronary
C.S.	79	M	130/80	4 yrs.	?	nodular	III	57	gangrene-leg
E.C.	80	M	130/80	1 mo.	no	none	I	?	pyelonephritis

TABLE II--NONDIABETIC PATIENTS

Pt.	Age	Sex	B.P.	NPN	Adrenals	Cause of Death
L.T.	16	M	132/90	263	II	ch. glomerulonephritis
V.A.	19	M	100/70	100	II	pulmonary infarctions
R.W.	24	M	180/120	250	II	ch. pyelonephritis
R.R.	25	M	170/120	277	II	ch. pyelonephritis
M.S.	27	M	159/108	159	III	ch. glomerulonephritis
M.B.	29	F	180/107	240	II	ch. glomerulone phritis
I.N.	29	F	174/140	?	II	ch. glomerulonephritis
C.D.	36	M	268/144	178	III	nephrosclerosis
I.S.	43	F	240/140	272	IV	nephrosclerosis
R.B.	45	M	260/120	128	IV	ch. glomerulonephritis
F.S.	51	F	190/140	?	III	congestive failure
M.B.	54	F	178/130	90	I	congestive failure
S.F.	56	F	246/148	?	III	congestive failure
K.T.	56	M	128/80	43	I	coronary
M.E.	59	F	122/88	35	II	coronary
A.R.	60	M	152/50	64	I	ASHD, coronary
O.S.	60	M	240/120	131	I	subac. glomerulonephritis
A.H.	69	M	70/0	46	III	coronary
F.J.	76	M	140/87	240	II	ch. pyelonephritis
J.M.	76	M	174/120	128	IV	ac. pyelonephritis

DISCUSSION.

As shown in Tables I and II the patients studied varied in age from 16 to 80 years with quite similar distribution in both the diabetics and the nondiabetics. Those with diabetes had had the disease from a few weeks to 27 years. Most of these patients--diabetics and nondiabetics--had been ill for quite a long period of time and tended to have a prolonged downhill clinical course to their death. Only 10 of the 60 patients had a terminal episode lasting less than one week. The adrenals from these 10 patients were evenly distributed in the four described grades of lipoid vacuolization, so the cause of death probably had very little influence on the lipoid deposits in the adrenal cortex.

When the adrenal cortices of all the patients are graded as to the relative amount of vacuolization, it can be shown graphically that there is a similar pattern in the diabetic and nondiabetic patients. Graph I indicates that the diabetic process itself probably does not alter the histopathology of the adrenal cortex to any degree.
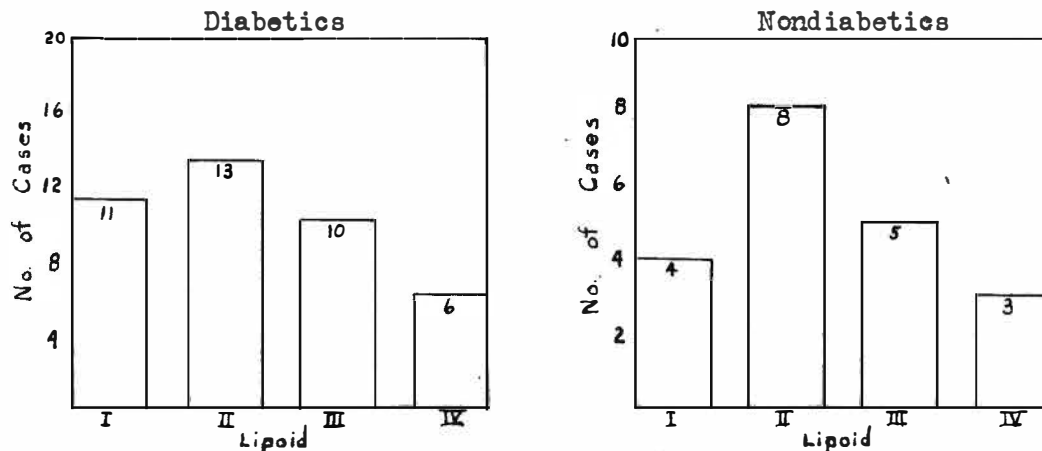
Graph I. Comparison of the degree of vacuolization of the adrenals in diabetic and nondiabetic patients.

When the patients are divided as to their sex, it can be shown in Graphs II and III that there is no essential difference in adrenal vacuolization in either sex, whether diabetic or nondiabetic. More of the males fall in grade II in both the diabetics and nondiabetics, but the overall pattern does not seem to be altered by sex alone.
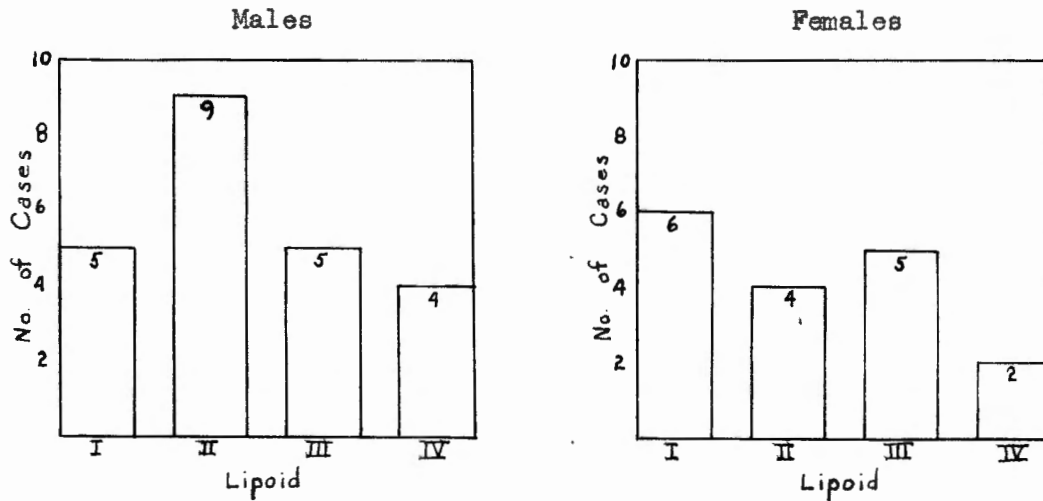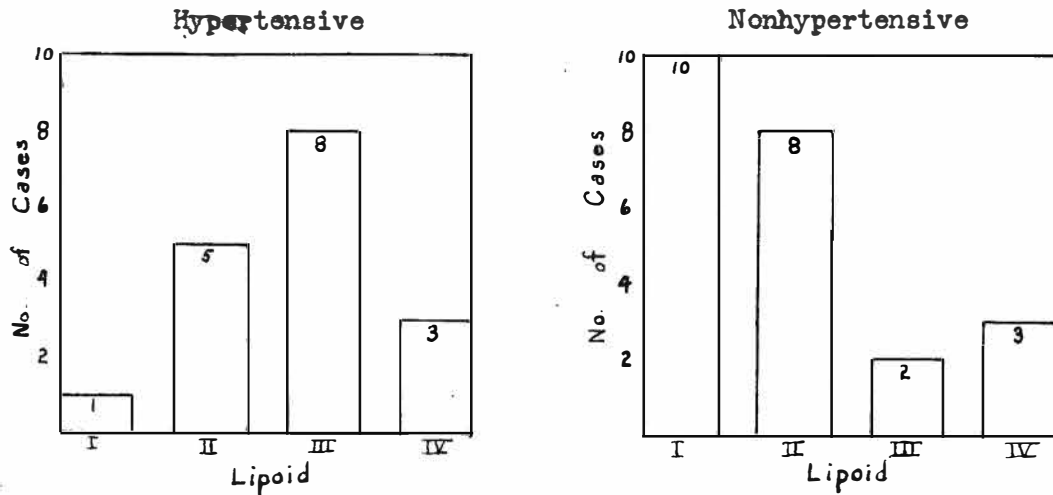

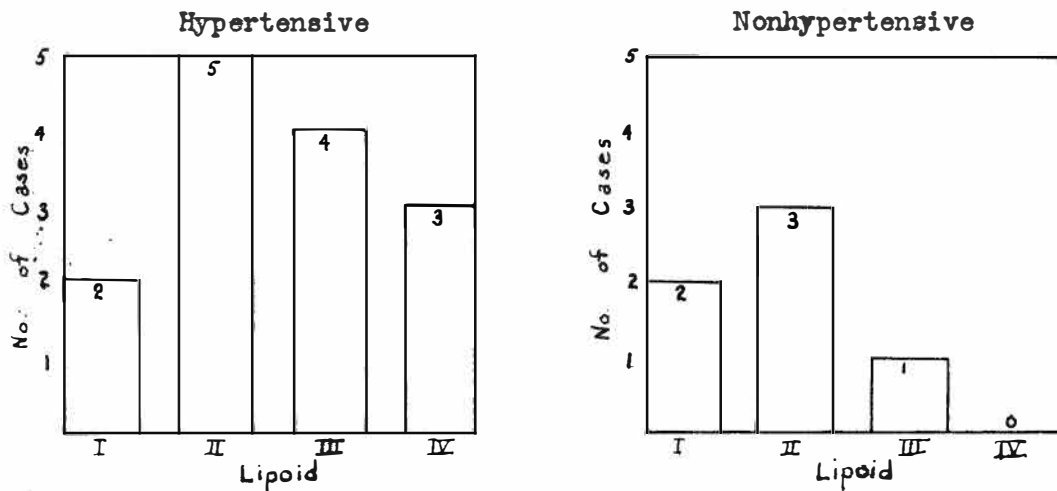Graph II.   Comparison of the degree of adrenal vacuolization in male and female diabetic patients.
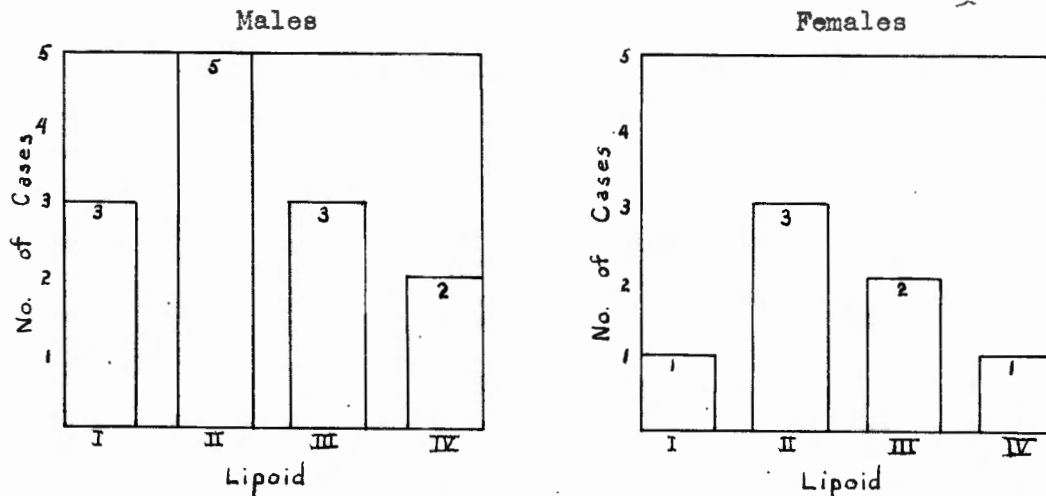
Graph III.   Comparison of the degree of adrenal vacuolization in male and female nondiabetic patients.

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If the hypertensive patients, systolic above 160 mm. Hg. and/or diastolic above 90 mm. Hg., are compared to the nonhypertensive group, it is seen that the hypertensive group tends to show more vacuolization both in the diabetics and in the nondiabetics (Graphs IV and V). This would agree with previous studies showing excessive lipoid deposits (80-82) and increased phosphomolybdate reducin substances in the urine (60) of hypertensive patients.
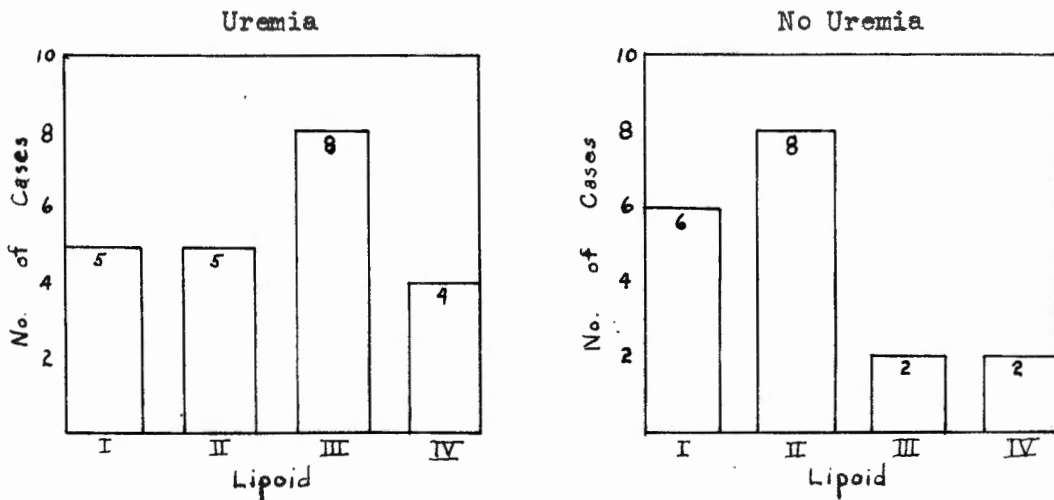
Graph IV. Comparison of the degree of adrenal vacuolization in hypertensive and nonhypertensive diabetic patients.

Graph V. Comparison of the degree of adrenal vacuolization in hypertensive and nonhypertensive nondiabetic patients.

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Since so many of these patients had serious kidney disease, the adrenals from those who showed nonprotein nitrogen levels over 60 mg.% and/or severe kidney disease by microscopic sections were compared with the adrenals from the patients with no evidence of any kidney disease. In both the diabetics and nondiabetics there seemed to be some increase in the lipoid deposits in the adrenal cortices from the uremic patients, but the difference is not marked (Graphs VI and VII).
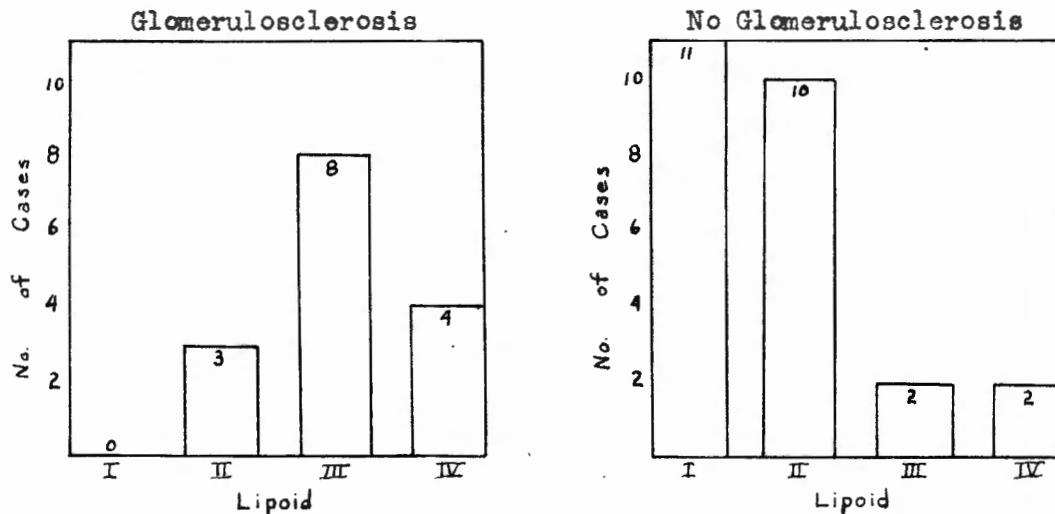

Graph VI. Comparison of the degree of adrenal vacuolization in uremic and nonuremic patients with diabetes.
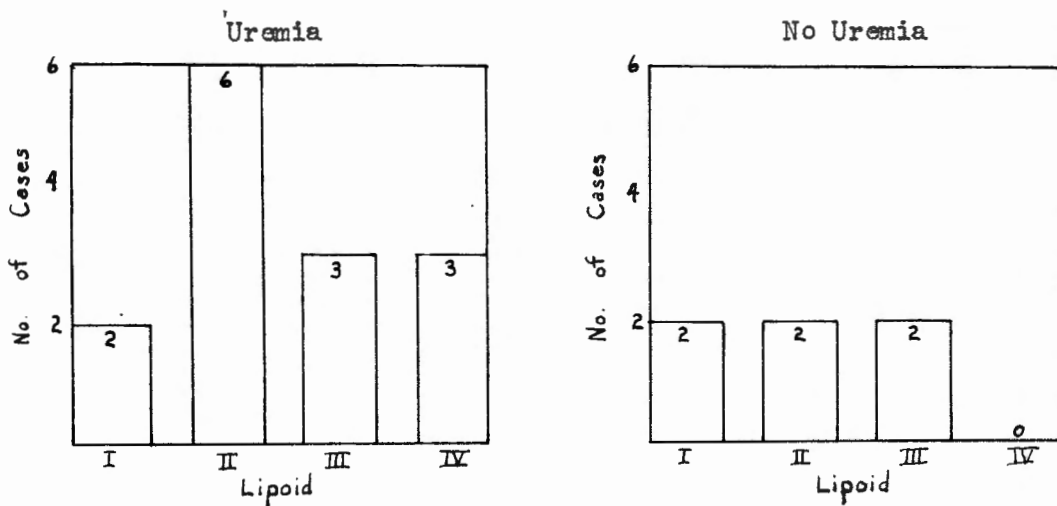
Graph VII. Comparison of the degree of adrenal vacuolization in uremic and nonuremic patients without diabetes.

The adrenal glands from the diabetics with intercapillary glomerulosclerosis showed a marked increase in lipoid vacuolization as compared with the glands from diabetics without definite kidney lesions (Graph VIII). Of the 15 patients with definite glomerulosclerosis 12 fell in group III or IV while 21 of the 25 diabetics without glomerular lesions fell in groups I and II. These differences in the degree of lipoid deposits agree very well with the findings of Becker (11).
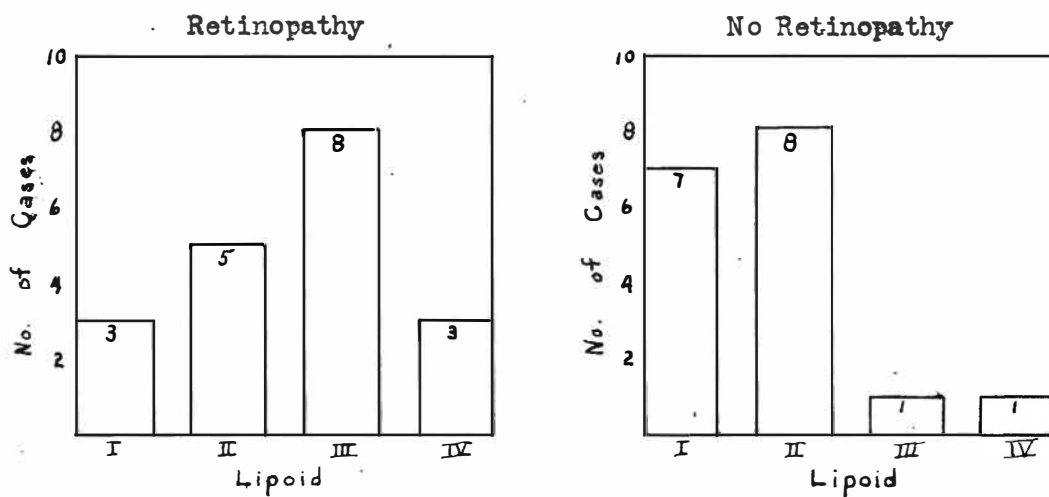

Graph VIII. Comparison of the degree of adrenal vacuolization in diabetic patients with and without glomerulosclerosis.

The finding of increased vacuolization in the adrenals from patients with glomerulosclerosis might be explained on the basis of hypertension and uremia combined. However such does not explain why the five patients without hypertension and two patients with no particular evidence of uremia should also show this increased amount of lipoid material. The best correlation in the small number of patients seems to be with the glomerular lesions themselves.

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Since the retinal lesions seem to be so closely related to the kidney lesions, then the adrenals from the patients with diabetic retinopathy should also show increased vacuolization. This was more difficult to evaluate since the retinopathy was based on clinical findings which were not always adequately described in charts. Only two of the patients with glomerulosclerosis were not described as having diabetic retinopathy, but both of these patients had such advanced cataracts that the retinae could not be seen. Of the 19 patients with rather definite diabetic retinopathy, 6 showed no evidence of glomerular capillary disease. It can be seen from Graph IX that there are increased lipoid deposits in the patients with retinopathy, but the difference is not as marked as was found in the glomerular lesions.

Graph IX. Comparison of the degree of adrenal vacuolization in diabetic patients with and without diabetic retinopathy.

No definite conclusions can be drawn from this study since it includes such a small number of patients. However it does substantiate

the findings of other authors as discussed earlier in the introductory remarks. Capillary complications tend to be found in diabetics who have had the disease for a number of years and who were under rather poor control. Yet other diabetics who had had the disease for long periods of time under poor control showed no capillary lesions. The best correlation seemed to.be reflected in the adrenal cortices. The adrenal glands from patients with capillary lesions and in particular those with glomerular disease showed the greatest amount of lipoid deposits in the cortices. The question now arises what this degree of vacuolization means as far as the activity of the gland is concerned.

Numerous authors have studied the adrenal glands in correlating the histopathology with the activity (80-91). All of these studies come to quite similar conclusions. The lipoid deposits in "normal" adrenal glands removed from a young adult or from rats are mostly confined to the outer half of the zona fasciculata with less in the zona glomerulosa and still less in the inner portion of the fasciculata and in the zona reticularis. By the use of special staining techniques the lipoid material has been shown to be mostly cholestrol and its derivatives. The lipoid of the inner areas also contains some triglycerides. Since the active hormones themselves cannot be shown directly, the activity of the gland then is determined mainly by the amounts of cholesterol derivatives present. The amount of this material and the changes in the cells have been shown to correlate well with adrenal hormonal activity.

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If the adrenal gland receives a sudden stimulation by sudden stress, acute infection, or a corticotropin injection, there is a rapid depletion of the lipoid storage within the cells. Apparently the active hormones or their precursors within the cells are discharged, thus depleting the storage supply of lipoid. Lipoid storage slowly returns to normal in the cells after the sudden stimulation is released. There may be a small increase in the size of the gland as there is some stimulation to hypertrophy.

If stimulation persists over a prolonged period of time by repeated injections of corticotropin or by prolonged severe stress, there is again seen the initial decrease in the vacuolization of the zona fasciculata. As the animal begins to adapt himself to this stressful situation, the gland begins to increase its supply of lipoid and continues to do so until there is more than the normal supply of lipoid within the cells. In Selye's theory of adaptation this is the stage of resistance (81). These animals continue to have the stressful stimulation which causes increased hormonal release, but the glands are also able to produce more lipoid stores than normal. If this process continues, the gland eventually becomes exhausted with loss of the lipoid deposits and atrophic changes in the cells which usually results in the death of the animal.

If the pituitary gland is unable to produce corticotropin to stimulate the activity of the adrenal gland, the lipoid again tends to decrease and becomes inactive. These adrenal glands likewise become atrophic and do not change when subjected to stressful situations.

In interpreting the adrenals studied in this paper the normally active gland would probably be placed between groups II and III. The adrenals in groups I and II which show decreased vacuolization must have been under sudden stressful conditions or have been under prolonged decrease in corticotropin stimulation. Since very few of these patients had any history of any sudden terminal stress, it is more likely that they had been under very little pituitary stimulation. Those adrenal glands in groups III and IV where there were increased amounts of lipoid deposits present must have been under prolonged pituitary stimulation from some type of stressful situation. If this is true, the glands in group IV probably were producing more of the active hormones than were the other glands.

Such prolonged corticotropin stimulation might be caused by long periods of poor control. Without the insulin to control the diabetes well, the patient was placed in a stressful situation which eventually caused the increased lipoid deposits. This still does not explain why other patients who were also under similar stress did not show the increased deposits nor the capillary lesions. There is a good correlation between the capillary lesions and the increased vacuolization of the adrenal cortex, but more study is needed before any definite explanation can be made of this phenomenon.

SUMMARY.

1. The biggest problem in clinical diabetes today is the prevention and control of the vascular complications. Among the most important of these are the capillary lesions of the retina and the

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glomerulus. The retinal lesions which are basically capillary micro-aneurysms with associated hemorrhages and waxy exudates are a common cause for loss of eyesight among the diabetics. The more serious kidney lesions which may be in a specific nodular form or in a more nonspecific diffuse form have become an increasingly common cause of death in the diabetic and particularly the juvenile diabetic.

2. Many attempts have been made to find the cause of these capillary lesions. They are quite specific for diabetes, but some other factor must also be present. Long duration and poor control of the diabetic process are among the most commonly associated historical findings in patients with the capillary lesions. In recent years it has been found that increased adrenal cortical activity may be an important factor in the etiology and progression of these lesions. Most patients with capillary disease show evidence of increased adrenal cortical activity; hypophysectomy or adrenalectomy have been used with some success in preventing the progression of the lesions; and similar lesions have been produced in experimental animals by injection of cortisone.

3. In this paper 40 diabetic patients and 20 nondiabetics who came to autopsy during the past 10 years were studied as to the difference in the histopathology of their adrenal glands. Studies were made to see whether diabetes, sex, hypertension, uremia, diabetic retinopathy, or intercapillary glomerulosclerosis had any influence on the degree of lipoid vacuolization within the cells of the adrenal cortex. The best correlation seemed to be with the diabetic retino-

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pathy and glomerulosclerosis although there was also some correlation with hypertension and uremia.

4. The increased lipoid deposits found in the adrenals from diabetics with capillary lesions follow the patterns of adrenals which have been under prolonged stressful stimulation with resultant increase in hormonal activity. Although no definite conclusions can be reached, it is apparent that there is a difference in the adrenal activity in the patients with capillary disease as compared to those without any diabetic capillary disease.

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PLATE I

Figure 1.   Kidney section from a 51 year old woman who had had dia-
            betes for 5 years.   This glomerulus shows several nodular
            lesions which are so typical of intercapillary glomerulo-
            sclerosis (X 337).

Figure 2.   Kidney section from a 22 year old man who had had diabetes
            for 14 years.   This glomerulus shows the diffuse thickening
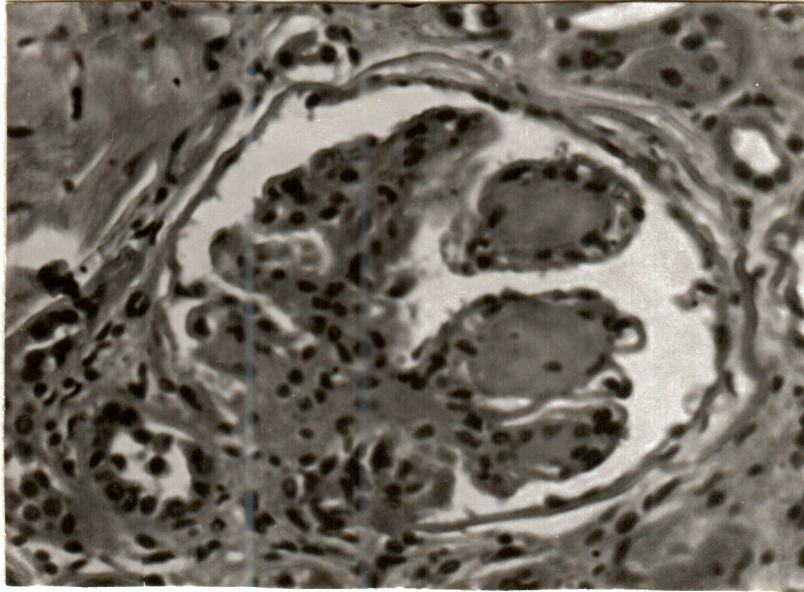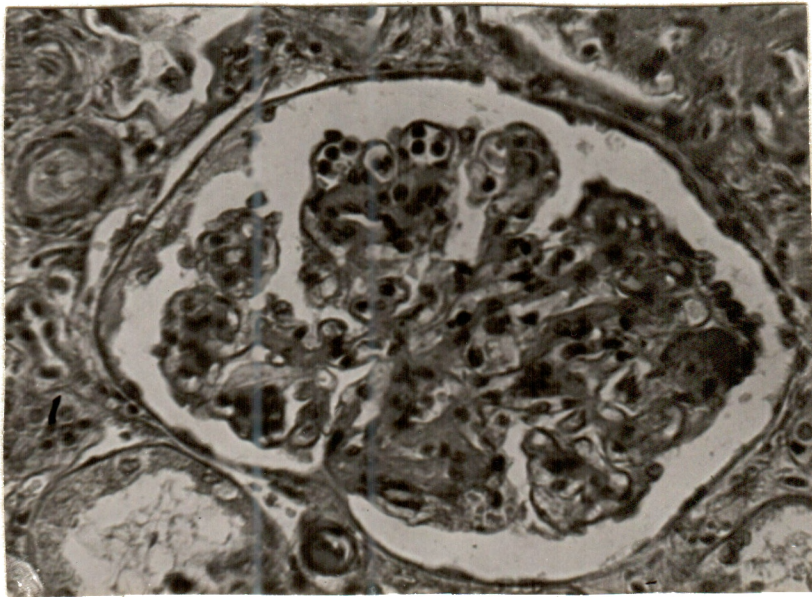   of the capillary walls with dilatation of some of the capil-
            laries (X 337).

PLATE I

Figure 1

Figure 2

PLATE

Figure 3. Adrenal section class fied as grade I from a 59 year old diabetic woman who died from rapidly progressive liver disease. The cells throughout the zona fasciculata are small and homogeneous in appearance without any evidence of lipoid vacuolization (X 91).

Figure 4. Adrenal section classified as grade II from a 53 year old diabetic woman who died from myocardial infarcts and congestive heart failure. The cells in the upper portion of this slide are small and homogeneous as shown in Figure 1 above, but an area of lipoid-fil_ed cells can be seen in the lower left portion of the photomicrograph (X 91).
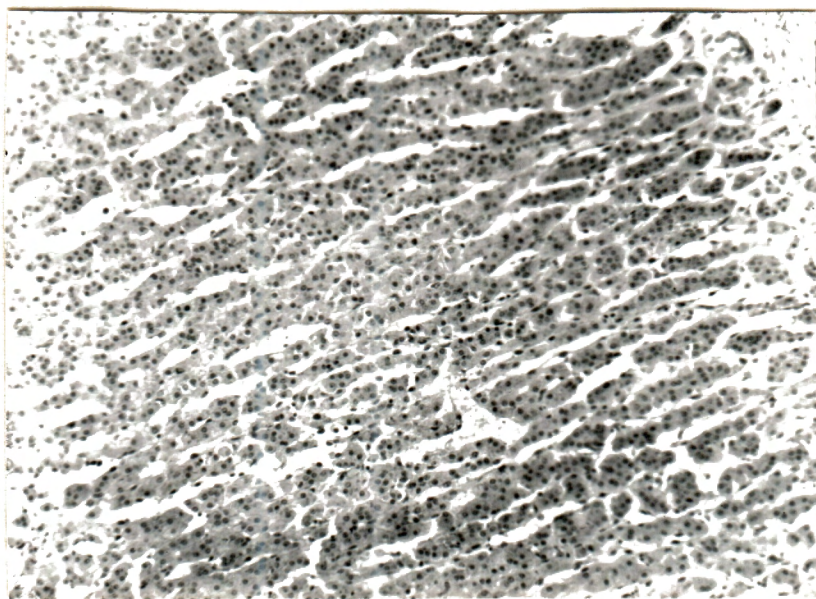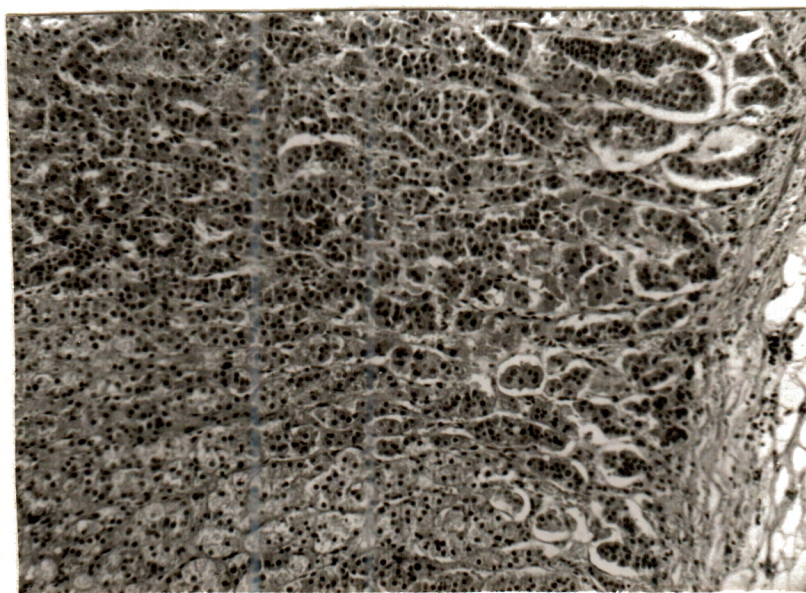
PLATE II

Figure 3

Figure 4

PLATE III

Figure 5. Adrenal section classified as grade III from the 22 year
old male patient with the diffuse glomerulosclerosis as
shown previously (Figure 2). This section shows diffuse
lipoid-filled cells extending to the zona reticularis on
the left, but there is very little lipoid in this latter
area (X 91).

Figure 6. Adrenal section classified as grade IV from a 47 year old
diabetic man who had no kidney disease and who died from a
myocardial infarct. This section shows diffuse lipoid
vacuolization of the cells throughout the adrenal cortex
with no differentiation into the various zones (X 91).
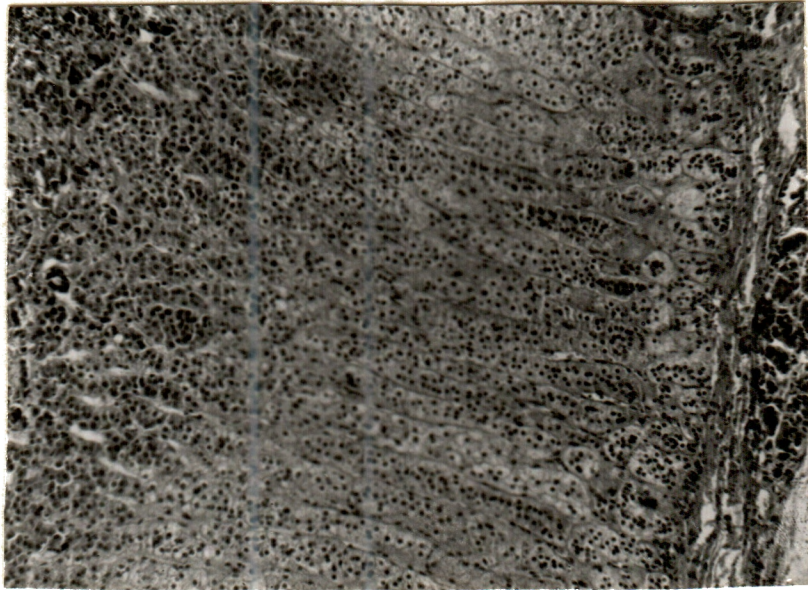
PLATE III

Figure 5

Figure 6

PLATE IV

Figure 7. This photomicrograph shows an unusual view of the kidney
and adrenal cortex from the 51 year old woman with inter-
capillary glomerulosclerosis whose lesions were shown in
Figure 1. On the right can be seen the typical nodular
lesion in one of the glomeruli with the grade IV vacu-
olization of the adrenal cortical cells extending to the
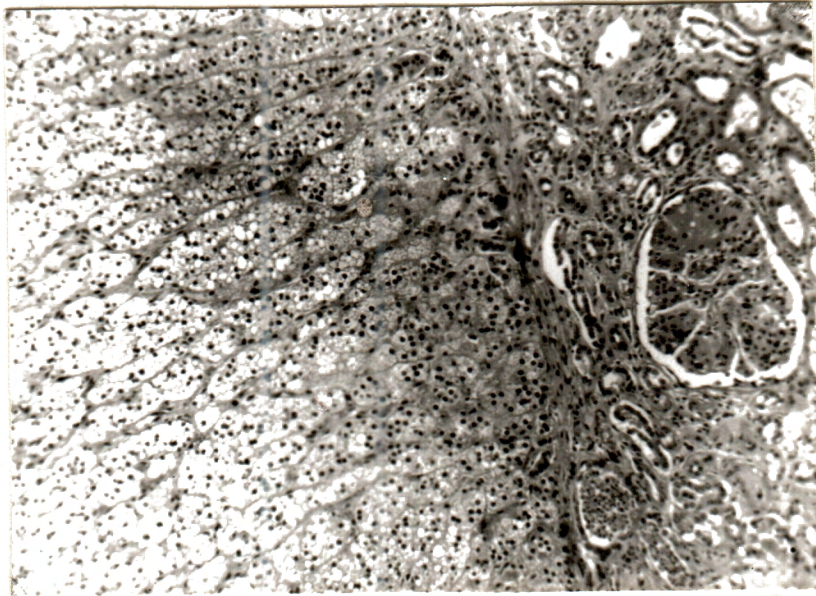left (X 91).

PLATE IV

Figure 7