Pathologic Findings and Laboratory Data in a New Strain of Obese Hypertensive Rats

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A new strain of rat characterized by genetic obesity, endogenous hyperlipidemia, and hypertension was obtained in this laboratory. The abnormal phenotype is inherited as a homozygous recessive trait. The animals exhibit marked hypertriglyceridemia, moderate hypercholesterolemia, and an electrophoretic pattern resembling that of human Type IV hyperlipoproteinemia. The average life-span is less than 1 year, due largely to the development of premature renal and vascular disease. The kidney lesion has both glomerulonephritic and nephrosclerotic components and is accompanied by marked proteinuria. About 12% of animals develop urinary tract calculi. The vascular disease consists of fibrous and fatty-fibrous intimal plaques, and polyarteritis. The obese animal offers a useful model for investigating abnormal lipid metabolism and the etiology and pathogenesis of atherosclerosis. (Am J Pathol 80:129–142, 1975)

A NEW STRAIN of rat characterized by genetic obesity, hypertension, and endogenous hyperlipidemia was recently developed in this laboratory. As previously described,[1] the abnormal animal was obtained by mating a female spontaneously hypertensive rat derived from the Kyoto Wistar strain [2] with a normotensive Sprague-Dawley male. The genetically obese animal appeared after several generations of selective inbreeding of hypertensive offspring of the original cross.

The abnormal phenotype was due to a single recessive gene (*f*) which probably resulted from a genetic mutation. This gene exists along with its dominant or wild form (*F*) in allele pairs which are heterozygous or homozygous. When 2 rats that each carrying the same recessive gene in heterozygous condition (*Ff*) mate, about one-fourth of their offspring will be obese and homozygous (*ff*) for the injurious gene. Seventy-five percent of offspring will present a normal phenotype; of these, 50% carry the injurious gene in heterozygous condition (*Ff*) and the remaining 25% are homozygous dominant (*FF*). At present, the heterozygous parents required to produce abnormal offspring can be identified only by the presence of obese rats in their litter.

One hundred and four obese rats (55 females and 49 males) have now

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been studied over their lifetimes, and the object of this report is to present the main pathologic lesions, abnormal laboratory findings, and cause of death in these animals.

Materials and Methods

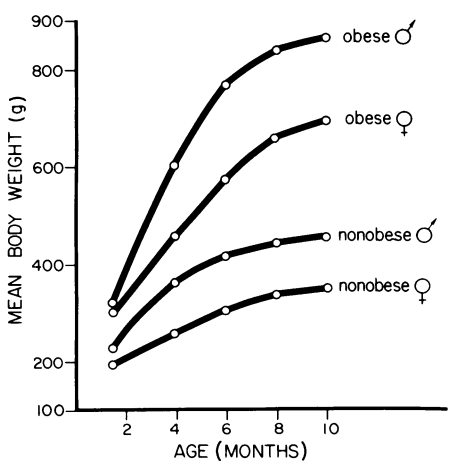
Both obese rats and their nonobese siblings were studied. The animals were housed in individual cages in air-conditioned rooms. The diet consisted of Purina chow *ad libitum* and tap water for drinking. Body weight was recorded weekly starting at about 4 weeks of age. Daily consumption of food was determined periodically with use of metabolism cages. The blood pressure was measured monthly under Nembutal anesthesia by inserting a polyethylene catheter into the femoral artery and attaching it to a mercury manometer. After an overnight fast, the levels of plasma cholesterol and triglycerides were determined by Autoanalyzer after isopropanol extraction of interfering substances. Serum electrophoretic patterns were obtained with the polyacrylamide gel technique (Canalco, Rockville, Md.). Plasma levels of urea nitrogen, glucose, and electrolytes were determined on a multichannel Autoanalyzer. Plasma proteins were determined by the biuret reaction [3] using a Beckman DU colorimeter. Proteinuria was measured qualitatively with Labstix and quantitatively according to the method of Shevky and Stafford.[4] The presence of glycosuria was established by use of Benedict's reagent.

Necropsies were performed on all rats at the time of death or sacrifice, and after the gross lesions were identified, microscopic sections of various organs were prepared with hematoxylin and eosin stain and, in the case of vascular lesions, also with elastic Van Gieson and oil red O stains.

Results

Body Weight and Obesity

Animals were first identified as genetically obese at about 5 weeks of age, when they showed visible widening of the lower trunk. Thereafter, the body contour became progressively more rotund (Figure 1). There was enormous deposit of fat subcutaneously, retroperitoneally, and in the



TEXT-FIGURE 1—Body weight of obese rats; mean of 25 rats at each age interval.

mesentery. Body weight increased rapidly, rising in males from a mean of 250 g at 5 to 8 weeks of age to 450 g at 3 months and to 700 g at 5 months. Animals 7 to 12 months old often attained weights of 750 to 1000 g. Males were heavier than females at practically all ages (Text-figure 2).

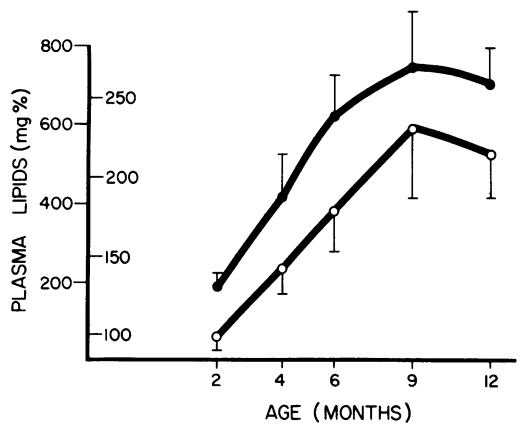
After about 6 months of age, the animals showed ruffing and discoloration of the fur which was more marked in males than in females. The latter were uniformly cleaner than males in external appearance. Some rats developed a decubitus type of ulcer and infection of the skin in the pubic and/or cervical regions, probably as a result of pressure from obesity.

Hyperphagia

The food intake of obese rats was twice and, in some instances, two and one-half times that of their nonobese siblings.

Hyperlipidemia

The obese animals uniformly developed hyperlipidemia which was characterized by a marked rise in plasma triglycerides and a moderate rise in plasma cholesterol. When first obtained at 5 to 8 weeks of age, plasma triglycerides were already elevated to a mean level of 180 mg% and plasma cholesterol to 96 mg%. Subsequently, the triglycerides rose progressively to mean levels of 425, 620, and 750 mg% at 4, 6, and 9 months of age, respectively, while the mean plasma cholesterol at the same intervals was 144, 186, and 220 mg% (Text-figure 2). Several animals between 6 and 10 months of age attained very high triglyceride values, i.e., 4400 to 7600 mg%. As the hyperlipidemia increased, the plasma changed from slightly cloudy to turbid and finally became milky. Both plasma triglycerides and cholesterol declined terminally during the interval of anorexia and weight loss which preceded death.



TEXT-FIGURE 2—Plasma lipids (mean ± SD); N = 15 at each age interval. (Triglycerides, *solid circles;* cholesterol, *open circles*)

Elevation of plasma lipids was not as marked in female as in male rats although there were exceptions, especially in later life when the females often attained a comparable grade of hyperlipidemia.

Gel electrophoresis usually showed a slight to marked increase in pre-β-lipoproteins and a weak or absent β band. Chylomicrons varied widely from absent or weak to increased, while α-lipoproteins were uniformly increased.

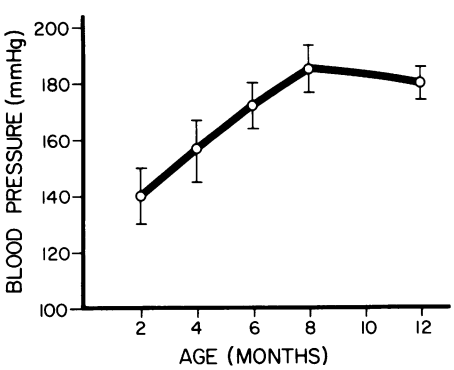
The nonobese rats did not develop hyperlipidemia. In 35 animals between 2 and 14 months of age, plasma cholesterol levels ranged from 50 to 110 mg% with a mean of 65 and plasma triglycerides from 10 to 75 mg% with a mean of 42.

Hypertension

Text-figure 3 shows the blood pressure of obese rats at various age intervals. The earliest readings were obtained at 6 to 8 weeks of age, at which time most animals were either in a prehypertensive stage or were already hypertensive (blood pressure, 150 mmHg or more). Thereafter, as a rule the blood pressure rose progressively, and the mean levels were 154, 187, and 182 mmHg at 4, 8 and 12, months, respectively. An occasional rat remained either at borderline hypertensive levels throughout life or failed to become hypertensive. There was usually a drop in blood pressure during the terminal interval of anorexia and weight loss exhibited by most animals.

Metabolic Abnormalities

Although the data in these areas are incomplete at present, the obese animals appeared to have defects in carbohydrate and protein metabolism. Elevated levels of blood sugar and, at times, glycosuria were detected in some rats and attributed to increased glucocorticoid activity



TEXT-FIGURE 3—Blood pressure (mean ± SD) of obese rats; N = 15 at each age interval.

which inhibits peripheral utilization of glucose. This is likely to be associated with secondary hyperinsulinism. Since excess glucocorticoid also reduces the rate of protein synthesis, it is anticipated that the animals will exhibit increased levels of amino acids in the blood which should give rise to gluconeogenesis. The animals probably convert both glucose and amino acids to fatty acids which are utilized as a source of energy and deposited in the body in excessive amount. As a rule, the livers of obese rats showed extensive fat infiltration.

Endocrine Glands

No significant gross lesions have been observed in the pituitary, adrenals, pancreas, thyroid, and gonads. The parathyroids showed no significant gross or microscopic change. Only the adrenals appeared to be enlarged, but this was difficult to establish in relation to body weight. Microscopically, the zona fasciculata of these glands was prominent, and its cells contained abundant lipid. The anterior lobe of pituitary showed a preponderance of basophil cells.

Detailed information regarding endocrine function in obese rats is not available. Increased levels of plasma corticosterone were reported previously,[1] although whether this represents a primary hypersecretion of the adrenals or is secondary to increased production of ACTH either by the pituitary or because of a hypothalamic lesion is not known. Thyroid function has not been investigated.

Some animals have shown hyperglycemia and glycosuria, and this, along with the observation at autopsy of giant hyperplasia of the islets of Langerhans, indicates pancreatic dysfunction.

Both male and female animals have failed to produce offspring when mated with each other or with nonobese rats. However, microscopic study has revealed the presence, in at least some animals, of spermatogenesis or of mature ovarian follicles with ova. Possibly, mechanical difficulty plays a role in the apparent sterility.

Proteinuria

All obese rats developed proteinuria. When first measured at 5 weeks of age the amount of protein in a 24-hour urine specimen ranged from 0.04 to 0.15 g. Thereafter, the proteinuria increased in severity, although not in a uniform manner. The qualitative urinary protein was 1+ at 5 weeks of age, generally rose to 3 to 4+ by 5 months, and then remained at this level for the rest of life. Obese male rats lost 0.1 to 0.4 g of protein daily at 4 months of age, 0.2 to 0.8 g from 5 to 8 months of age, and 0.3 to 0.9 g when 8 to 12 months old. The corresponding values for females were

lower, i.e., 14 to 40 mg at 2 months of age, 20 to 130 mg at 4 months, and 126 to 900 mg from 6 to 10 months. Later in life, however, females often excreted the same amount of protein as did males.

Loss of protein in the urine was accompanied by a corresponding fall in serum proteins and particularly in the level of plasma albumin. In a group of 12 obese rats with a daily proteinuria of 0.5 to 0.9 g, total serum proteins were reduced from predietary control levels of about 6.5 g% to 4.6 to 5.0 g%, while serum albumin declined to 2.6 to 3.2 g% from control values of 4.0 to 4.5%. However, none of the obese rats developed visible edema.

The nonobese siblings did not exhibit proteinuria. Numerous determinations on animals from 2 to 14 months of age showed daily amounts of urinary protein consistently below 50 mg and usually below 20 mg.

Kidney Disease

The proteinuria observed in obese rats was evidently due to increased permeability of the glomerular capillaries. It was present for several months before glomerular lesions could be clearly identified by light microscopy. Beginning at anywhere from 4 to 7 months of age, there was thickening of the capillary basement membrane followed by progressive development of focal necrosis, adhesions between adjacent loops and between loops and the parietal layer of Bowman's capsule, widening and increased cellularity of the mesangium, trapping of lipid droplets within the capillaries, and collagen deposition with hyalinization (Figure 2). There was hyperplasia of the cells lining the tubules, especially the proximal segments. Large numbers of protein casts were present within the tubular lumens. Destruction of glomeruli led to tubular atrophy, interstitial fibrosis, and increasing renal dysfunction. These changes were accompanied by progressive renal arteriolar lesions consisting of medial hypertrophy and hyperplasia, fibrinoid necrosis, intimal fibrosis, infiltration of lipid, and luminal narrowing; the resulting ischemia probably contributed to the onset of azotemia.

The combination of glomerular and vascular disease finally resulted in shrunken kidneys with symmetrically granular outer surfaces (Figure 3). Such kidneys were observed in some animals that were only 6 months old and were present to some degree in about 60% of all rats by the age of 10 months.

The nonobese siblings also developed granular kidneys. However, compared to obese rats, the disease was relatively infrequent, less severe, progressed slowly, and occurred much later in life. It was not present at all in rats less than 1 year old, and even in rats 12 to 20 months old the in-

cidence was about 15%, with only an occasional instance of azotemia.

Calculi were present in the urinary tract of 12 of the 104 obese rats. The stones varied from one to as many as 100 in number, were white, round, or irregular, usually firm to hard, and measured up to 1.5 cm in longest dimension. They occurred mainly in the kidneys and urinary bladder, especially the former, and were frequently associated with hydronephrosis and pyelonephritis (Figure 4). One or both renal pelves showed a number of tiny calculi or else the pelvis was filled with multiple small stones or a single large calculus. In some animals the pelvic cavity contained thick turbid fluid with abundant sediment.

Chemical analysis revealed that the stones consisted of calcium and ammonium–magnesium phosphates. Tests for carbonate, oxalate, uric acid, and cystine were negative. The plasma calcium and phosphorus levels of obese rats were elevated, and this may have predisposed to calculus formation. The mean plasma calcium level in 18 obese rats was 12 mg% (range, 8.8 to 16.5), and the mean plasma phosphorus level, 8.4 mg% (range, 4.3 to 16).

Urinary tract infection was occasionally present in the absence of calculi. In this instance, the urethra was a possible portal of entry for the bacteria since there was pressure on the pubic region from obesity and urinary contamination of the area.

None of the nonobese rats showed either calculus formation or pyelonephritis.

Cardiovascular Lesions

The heart usually appeared to be enlarged and presented a thick, firm left ventricular wall. However, hypertrophy could not be confirmed from the ratio of heart weight to body weight (cardiac index) because of the obese state of the animals. Occasionally, the muscle showed small, irregular, white foci which were visible through the epicardial surface. Microscopically these lesions consisted of myocardial necrosis with reactive fibrosis.

In the great majority of rats, the aorta showed no significant gross change. In several animals which died in uremia, the artery was rigid and contained palpable calcified transverse rings. Microscopically, oil red O stains usually revealed an increase in the content of lipid, which was present in fine droplet form, mainly extracellularly in the medial and intimal layers.

No lesions were detected grossly in the coronary arteries. On microscopic study these vessels showed slight smooth muscle cell

proliferation along with deposit of fat and, occasionally, calcium in the media or deep part of intima. No instance of well-developed intimal fibrous plaque, foam cell formation, or significant reduction in vessel lumen was encountered.

Gross vascular disease was observed at necropsy in 50 of the 104 obese rats, an incidence of 46%. The disease involved especially the pancreatic, superior mesenteric and hepatic arteries, and their branches. The vessels showed focal or diffuse nodular thickening, beading, and tortuosity and were often the seat of aneurysmal dilatation and thrombosis (Figure 5). The nodules varied from grayish-white or yellow to red and measured up to several millimeters in diameter.

Microscopically the principal lesion consisted of smooth muscle cell hyperplasia involving the medial and intimal layers. The proliferating fibers penetrated the intima and formed plaques composed of disordered layers of spindle-shaped cells contained in a compact or myxomatous stroma. Such plaques often projected into and reduced the vessel lumen. The proliferative change often destroyed the medial layer, leading to vascular dilatation and thrombosis. Both intimal and medial lesions contained abundant fat droplets in both extracellular and intracellular location. The fat tended to coalesce and to form globules or pools of fat, and at times this was associated with foam cell formation. Also, a number of lesions showed deposit of collagen and/or calcium, usually in the deep portion of intima (Figure 6).

Other arteries of obese rats often showed polyarteritis, in addition to fibrous or fatty-fibrous plaques. The polyarteritis was typical in structure except for the presence of abundant fat. Polyarteritis appears to be a characteristic response of the rat to the hypertensive state regardless of the etiology of the high blood pressure.

Arteriolar lesions similar to those in the kidneys were present frequently in other organs or tissues, especially pancreas, mesentery, adrenals, liver, and intestinal tract.

The nonobese rats also developed vascular disease which was similar in location and structure to that of obese animals. However, microscopically the fibrous plaques of nonobese rats contained a smaller amount of fat than those of obese animals and did not show lipid aggregates or foam cell formation. Also, the vascular lesions of nonobese rats developed much later in life. Prior to 1 year of age, gross vascular disease was present in less than 5% of nonobese rats as compared to over 40% of obese animals. However, among nonobese rats 12 to 20 months old the incidence had risen to about 35%.

Life-Span and Cause of Death

The obese rats lived about half as long as did their nonobese siblings. The average duration of life was 10.4 months, with a range of 8 to 14½ months. Females lived slightly longer than males, averaging 10.7 as compared to 10.1 months.

The short life-span of the obese animals was due to the development of renal and urinary tract disease, to complications of vascular disease, or to intercurrent infection. Forty-four of the 104 obese rats comprising the study died in uremia with BUN levels ranging from 104 to 250 mg%. Renal failure was due to glomerulonephritis and nephrosclerosis in 34 rats and to urinary tract calculi with obstruction in 10 additional animals. Nine rats died of ruptured abdominal aneurysm with massive hemorrhage, and 1 died of infarction of the small intestine and peritonitis due to thrombosis of the superior mesenteric artery. Death resulted from pneumonia in 22 rats. In 28 of the 104 animals, the cause of demise was not established with certainty at autopsy, even though there was a terminal downhill course lasting a few to several weeks and characterized by marked anorexia and weight loss. Some of the deaths in this category were possibly the result of metabolic disturbances, but if so, the nature of these was not clear.

Discussion

Zucker described a genetically obese rat strain which is similar to ours in many ways, i.e., genetic background, hyperlipidemia, proteinuria, and development of renal disease.[5-7] However, important differences are that the Zucker rat is not hypertensive nor does it develop vascular disease. As far as we know, our obese rat is the first laboratory animal which exhibits both spontaneous high blood pressure and elevated serum lipids.

The hyperlipidemia of the obese rats was endogenous in origin and not dependent on the amount of fat consumed. It developed uniformly in animals on a diet of Purina chow which has a relatively low fat content, i.e., about 5%. While the hyperphagia exhibited by the rats is undoubtedly necessary for the development of obesity and hyperlipidemia, it is not the basic cause of these derangements. Both resulted primarily from an inborn error in fat metabolism, the nature of which is not clear. Evidently, there is an imbalance between production of glycerides, probably by the liver, and their removal from the blood by adipose tissue. Production may be excessive and clearance inadequate, or production normal and clearance faulty. Most or practically all ingested food is converted to fat which is deposited in body stores.

High blood pressure is apparently the only genetic trait which the obese

rats share in common with their nonobese siblings. In neither case is the cause of the hypertension established. The high blood pressure occurs early in life and prior to the development of kidney disease. The same holds for the Japanese strain of spontaneously hypertensive rat which is one of the forebears of the obese rat.

The premature and frequent occurrence in obese rats of vascular disease of atherosclerotic type, especially fibrous or fatty-fibrous plaques, was probably due to the presence of both hypertension and hyperlipidemia. These are predisposing factors in the development of atherosclerosis in both humans and experimental animals. Although similar vascular lesions were observed in the nonobese siblings—which are hypertensive but not hyperlipidemic—the lesions occurred much later in life and were less frequent than in the obese rats. Also, vascular disease was absent in the genetically obese hyperlipidemic rat described by Zucker. The Zucker rat apparently becomes hypertensive only late in life after development of renal disease, whereas our rat has a primary form of hypertension which appears at a much earlier age. In the present study, the combination of high blood pressure and elevated serum lipid levels acting over a period of time complemented each other in promoting the premature development of atherosclerosis. Hence, this obese rat should serve as a useful laboratory model to explore the etiology and pathogenesis of atherosclerosis, perhaps especially by way of treatment or management designed to reduce or eliminate the hypertension and/or hyperlipidemia.

Kidney disease terminating in uremia was the most frequent cause of death among the obese rats. The renal lesion was manifest at a very early age by proteinuria which later was followed by progressive glomerular, tubular, and vascular damage. Similar glomerular and tubular lesions occurred in Zucker's genetically obese rat,[6] also in rats with hypothalamic obesity [8,9] or experimental nephrosis,[10,11] and also in senile rats [12-16]; the lesions were variously designated as glomerulonephritis,[8,15] glomerulonephrosis,[6,16] or nephrosis.[13] However, in all these situations renal arteriolar disease was either minimal in extent or absent or was not mentioned by the authors.

In a preliminary report,[1] the kidney disease in our obese rats was referred to as nephrosclerosis because of the presence of well-developed arteriolar as well as glomerular lesions. However, we now feel the disease has both glomerular and vascular components and that more likely the glomerular lesions which seem analogous to human membranous glomerulonephritis are primarily responsible for the destruction of nephrons, even though the process is hastened by the concurrent development of arteriolar disease.

Proteinuria, hypoalbuminemia, and hyperlipidemia coexisted in the obese rats, and the degree of proteinuria correlated directly and closely with the degree of hyperlipidemia. A comparable situation exists in both the human and experimental nephrotic syndrome. Drabkin [17] suggested that the hyperlipidemia in rats with experimental nephrosis might result from loss of albumin in the urine, which then stimulated excess production of albumin and lipoproteins by the liver. Perhaps this also applies to the genetically obese rat.[6] Rosenman *et al.*[18] had previously proposed that the hyperlipidemia of experimental nephrosis was initiated and maintained by loss of plasma albumin through the kidneys. However, other authors [19,20] questioned whether the proteinuria is the cause of the lipid disturbance, and there is even uncertainty as to whether hypoalbuminemia precedes [20,21] or follows [19] the hyperlipidemia in experimental nephrosis.

The obese rats were prone to develop urinary tract calculi. These occurred principally in the kidneys and/or urinary bladder and were usually associated with secondary obstruction to the flow of urine and with ascending infection and pyelonephritis. Chemically, the stones consisted of calcium and ammonium–magnesium phosphates. Calculus formation has not been observed in any of the nonobese siblings.

Elevated levels of calcium and phosphorus in the blood (probably resulting from demineralization of bone), hence, increased excretion of these elements in the urine, contributed to the formation of urinary tract stones. Another potential etiologic factor was the quantitative and perhaps qualitative changes in the urinary protein, which may have had ion-binding properties.

In addition to the areas of hypertension and of vascular and renal disease, this new strain of obese rat should prove useful for investigation of endocrine disorders, especially of the adrenals, pituitary, and pancreas, and of abnormalities in carbohydrate and protein metabolism. Abnormal glucose tolerance is frequently associated with Type IV hyperlipoproteinemia in the human. Also, a defect in carbohydrate metabolism might play a role in the development of endogenous hyperlipidemia.

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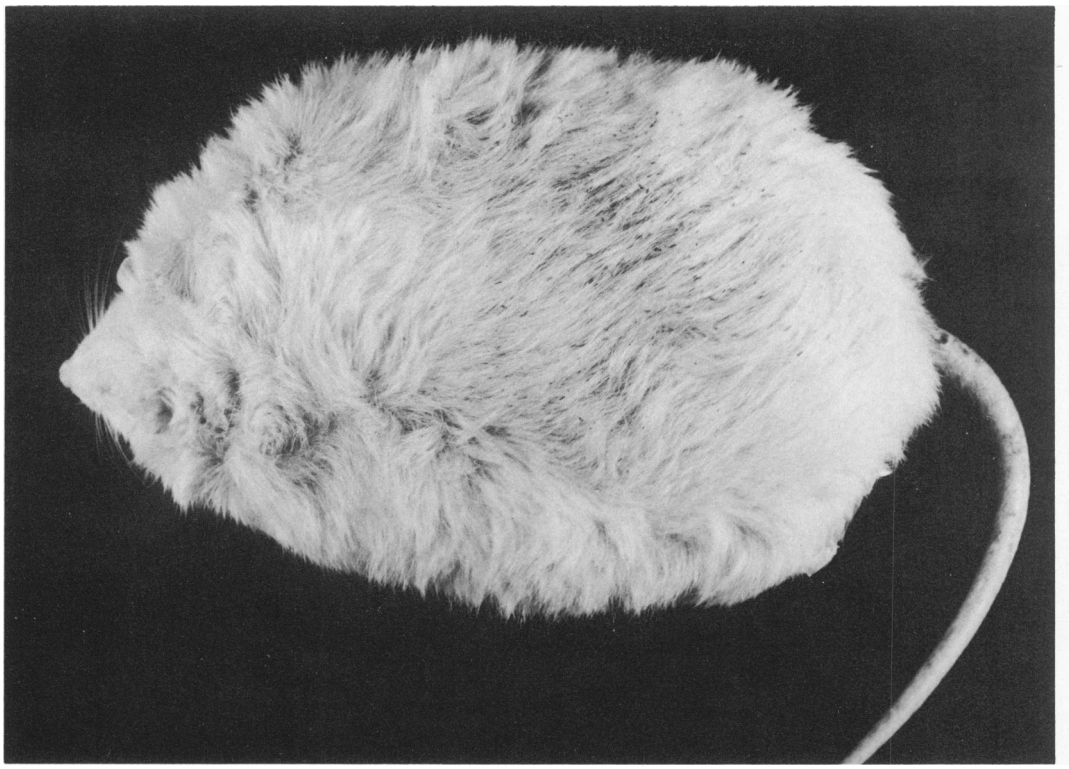


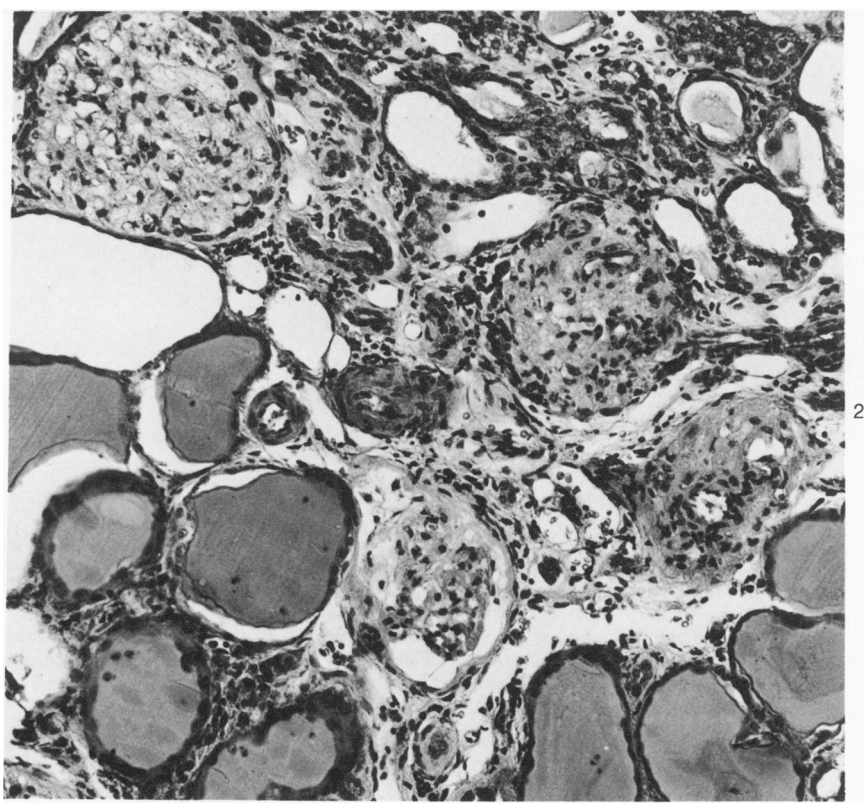
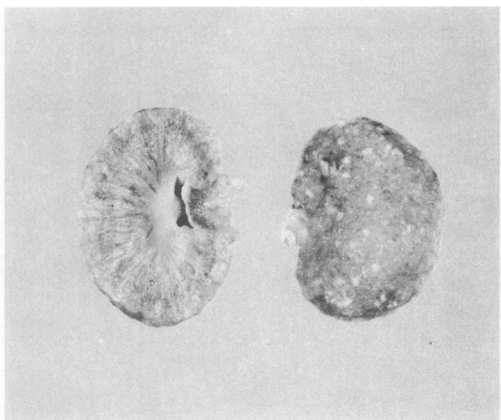
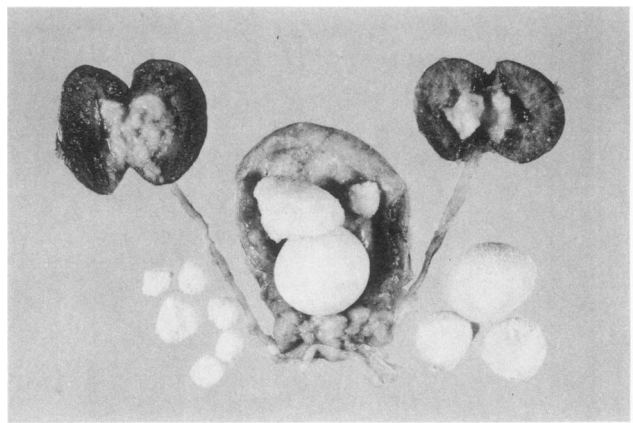
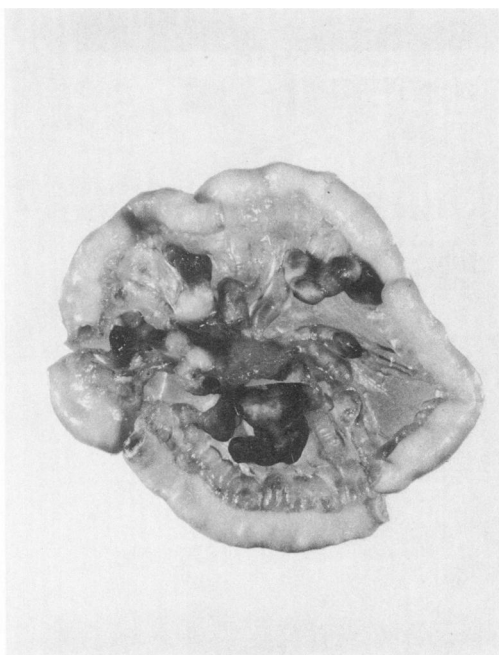


Figure 1—Obese rat at 10 months of age; note the ruffing and discoloration of the fur. **Figure 2**—Kidney with glomerular basement membrane thickening, adhesions, hyalinization, and lipid deposit; also note the marked thickening of the arterioles and tubular casts (H&E, × 170).







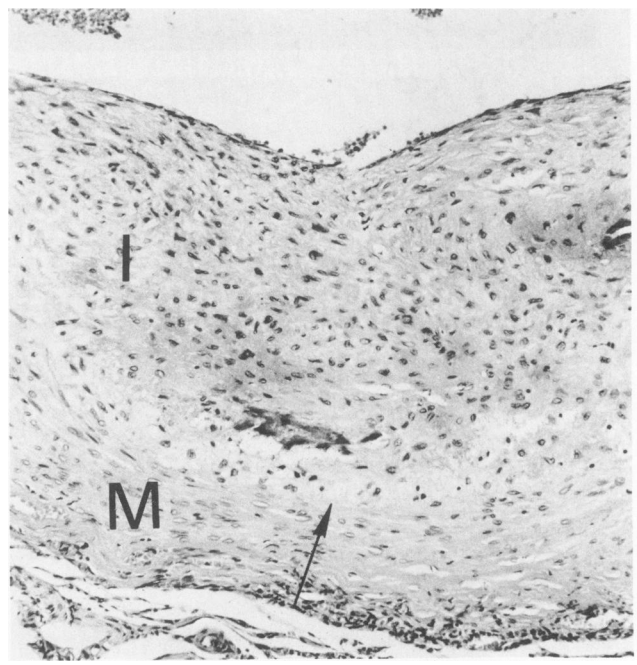


Figure 3—Granular kidneys in an obese 8-month-old rat. **Figure 4**—Calculi in kidneys and urinary bladder of 11-month-old obese rat. **Figure 5**—Vascular disease of mesenteric arteries with nodular thickening, ectasia, and thrombosis in a 10-month-old obese rat. **Figure 6**—Intimal fibrous plaque with lipid and calcific deposit (*arrow*) in pancreatic artery. *I* = intima, *M* = media (H&E, × 110).