there is as yet no conclusive evidence that the clinical manifestations in Refsum's disease are directly attributable to the accumulation of phytanic acid, although a causative role has not been ruled out. Our findings tend to strengthen the likelihood that the primary lesion affects an enzyme system that plays an important role in nerve cell function and that deletion or alteration of it leads to the nerve dysfunction. Thus, the accumulation of phytanic acid may, in a sense, be incidental and not of pathogenetic importance. The precise functional significance of the one-carbon degradation system in nerve tissue and of the alpha-hydroxy acids presumed to be formed by this mechanism is not known. We suggest that direct examination of nerve tissue for its alpha-oxidative capacity in other diseases of the nervous system may be fruitful.

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Hereditary Renal Disease in a Mutant Strain of Rats

Abstract. *Disease of the kidney developed in breeding stock of Gunn rats. The renal lesion is the result of a new mutation. The genetic defect is inherited as an autosomal dominant trait and is apparently lethal in the homozygous condition. The abnormality manifests itself as a congenital hydronephrosis with related cystic changes in the kidney.*

Inherited congenital hydronephrosis is a well-known clinical entity in man (*1*). This renal lesion has also been observed in laboratory animals (*2*). However, as far as we are aware, no colony of animals characterized by such pathology has been described. We now report the discovery of a new mutant strain of rats carrying a genetic disorder of the kidneys. The disorder was noticed in a colony of rats maintained by one of us (B.B.L.) at the University of Tennessee Memorial Research Center. Since the availability of a strain of rats with such a genetically controlled disorder would provide an experimental model for studies of renal pathophysiology and embryology, a colony was developed, and the mode of inheritance of the mutant was studied.

The genetic abnormality was found among the breeding stock of our colony of Gunn rats, which is a mutant of the Wistar strain of albino rats (*3*); it is characterized by the presence of jaundice secondary to the absence of bilirubin glucuronyl transferase activity in the liver (*4, 5*). Our colony of rats is derived from inbred Gunn rats (supplied in 1965 by Dr. R. L. Swarm of the University of Cincinnati). When the renal lesion was observed, a series of crosses was started to determine whether this anomaly was due to a new mutation or whether it was due to another expression of the gene responsible for the jaundice. For this purpose, four homozygous jaundiced male rats with renal lesions, detected by pyelography, were crossed to female animals heterozygous for the jaundice trait obtained from another colony of Gunn rats (provided by Dr. P. E. Zollman of the Mayo Clinic). These heterozygous female Gunn rats had normal kidneys as judged by pyelography and later by autopsy. The descendants from the original four pairs of animals were studied with pyelography and histological studies were frequently made after death. New crosses were made between siblings, as were backcrosses between the third and second generation, to analyze the inheritance of both traits (Fig. 1).

The occurrence of the kidney lesion was studied by macroscopic examination, histologic observation, and by pyelography. Urograms were carried out by injecting the contrast media (*6*) at a dose of 0.30 ml per 100 g of body weight. Films were taken at convenient intervals after the injection. A total of 976 kidneys was examined macroscopically, and 100 were examined microscopically; roentgenograms were obtained in 200 animals. The age of the rats ranged from 1 week to 1 year.

Three types of macroscopic lesions were observed (Fig. 2). Hydronephrosis was the most common abnormality (85 percent of the rats with kidney alterations). In rats exhibiting limited or moderate degrees of hydronephrosis, the kidneys appeared normal in size, with a smooth regular surface. In other animals, however, advanced hydronephrosis was found, and the kidney appeared as a translucent hydronephrotic sac with an irregular surface. On cut section, a multilocular cavity, which was separated into smaller subdivisions by incomplete trabeculas, was seen in the medulla and cortex. The hydronephrosis was unilateral in 60 percent and bilateral in 40 percent of the rats examined. In both cases, the enlargement of the renal pelvis was accompanied by dilatation of the ureter to variable degree with or without ureteral strictures. Despite the partial obliteration, the ureter was still patent, as demonstrated by pyelography and at autopsy. The ureters were normal in 25 percent of the

rats bearing moderate or advanced hydronephrosis.

The second type of lesion, seen in 5 percent of the rats, was characterized by solitary macrocysts, 1 to 3 mm in diameter, in the area between the renal cortex and medulla or in the cortex itself. A third type of injury observed in 10 percent of the rats consisted of cicatricial scars on the surface of kidney, leading, in some rats, to marked atrophy of the kidney. On cut section, these kidneys appeared compact. In one half of the rats with scars, hydronephrosis or visible cysts were also observed.

Microscopic examination of the kidney revealed four types of alterations: (i) cortical tubular dilatation (internal hydronephrosis type); (ii) tubular dilatation of the renal papillae; (iii) dilatation of the pelvis and calyces (external hydronephrosis type); and (iv) isolated microcysts in the renal cortex. In general, most of the kidney sections showed an association of at least two of the abnormalities, although in some specimens only one was found. The histologic picture of hydronephrosis was characterized by dilatation of the renal tubules, which were separated from each other by normal renal parenchyma (Fig. 2). Longitudinal sections of a tubular dilatation revealed closed sacs separated by an incomplete epithelial wall. Intercommunications between the cystic areas were a common finding. Similar alterations were also observed at times in the renal papillae. The characteristics of the tubular epithelium, as well as the examination of the connective tissue in rats with hydronephrosis, excluded degenerative or inflammatory processes. Isolated microcysts (200 to 300 μ in diameter) were observed in the normal renal parenchyma, as well as in the neighborhood of the internal hydronephrotic lesions.

Only one of these lesions (hydronephrosis) can be detected in the urograms. Nevertheless, as this lesion is present in most of affected animals, pyelography is a useful tool for identifying animals with kidney disease and for delineating the anatomical pattern of the urinary tract. The urograms of animals with unilateral or bilateral hydronephrosis showed a large dilated irregular renal pelvis and ureter in one (Fig. 3) or both kidneys respectively.

Genetic analysis of the data obtained after careful study of 488 animals in four generations showed that the renal lesion is inherited as an autosomal dominant trait. Among 307 descendants of crosses in which only one of the parents had a renal abnormality, 146 (47.5 percent) showed renal lesions, and 161 (52.5 percent) were normal. These results indicate a segregation ratio of 1 : 1 with $\chi^2 = 0.732$ ($P = .50$ to .30). When both parents had kidney abnormalities, irrespective of whether they were homozygous or heterozygous for the jaundice trait, the expected ratio for the inheritance of the kidney abnormality should be 3 : 1 (3 with kidney abnormality versus 1 normal) if both heterozygous and homozygous carriers for the kidney abnormality survive. The results observed, 119 (65.7 percent) with kidney abnormalities and 62 (34.4 percent) normal, differ significantly from those expected ($\chi^2 = 8.54$, $P = .01$).These results, however, suggest a proportion of 2 : 1, which can best be explained by assuming that the dominant gene is lethal in the homozygous condition. The χ^2 for this proportion is 0.024 ($P = .90$ to .80). The average size of litters was also reduced when both parents had the renal abnormality. Among 1200 newborns recorded, a mean of 7.68 $\pm$ 0.50 was observed in the crosses between two animals with kidney disease, while a litter size of 9.3 $\pm$ 0.47 was found when only one parent had the kidney lesion. This difference is significant ($P = .02$).

No linkage was found between the autosomal dominant gene causing the renal disease and the autosomal recessive gene responsible for the bilirubin glucuronyl transferase deficiency of the Gunn rats. This conclusion is based on observations in 240 descendants from cages in which all the males were homozygous and all the females heterozygous for jaundice, and in which only one of the parents had the renal abnormality. Sixty-one (25.4 percent) were homozygous, jaundiced with kidney lesions; 74 (37 percent) were homozygous without kidney lesions; 51 (21.2 percent) were heterozygous for jaundice and showed the renal abnormality; while 54 (22.4 percent) were heterozygous for jaundice and had normal kidneys.

The results demonstrate that the kidney lesions are not related to the abnormality causing jaundice. To our knowledge, diseases of the kidney have not been observed in Gunn rats, and the only renal abnormality reported in these animals is related to the deposition of

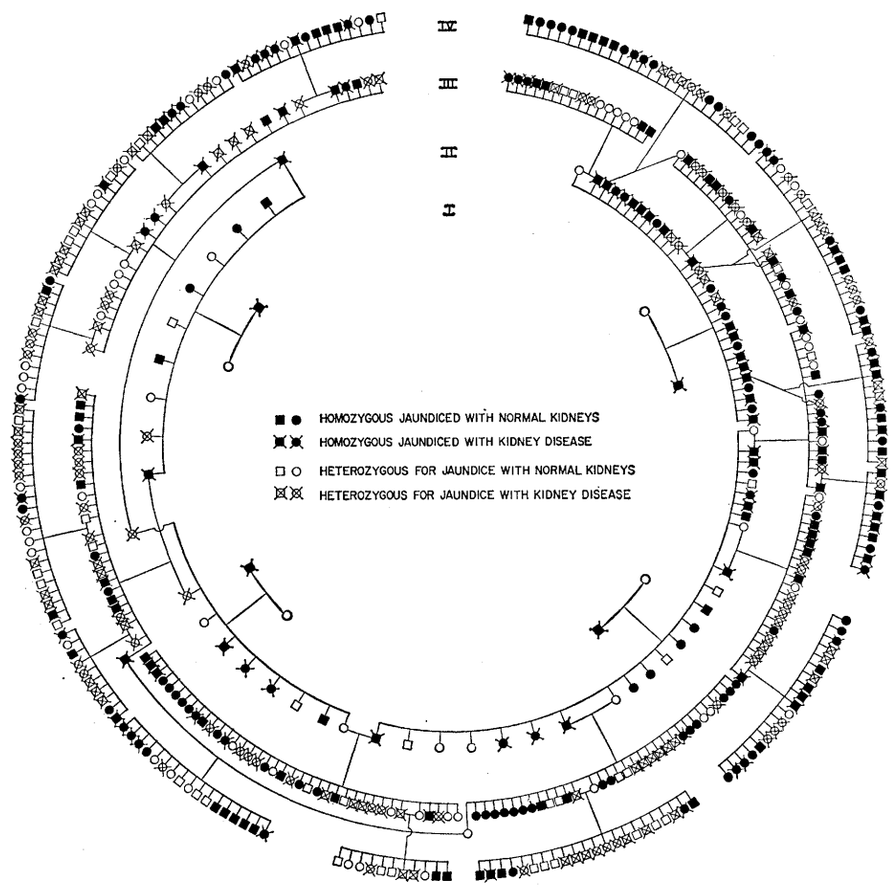
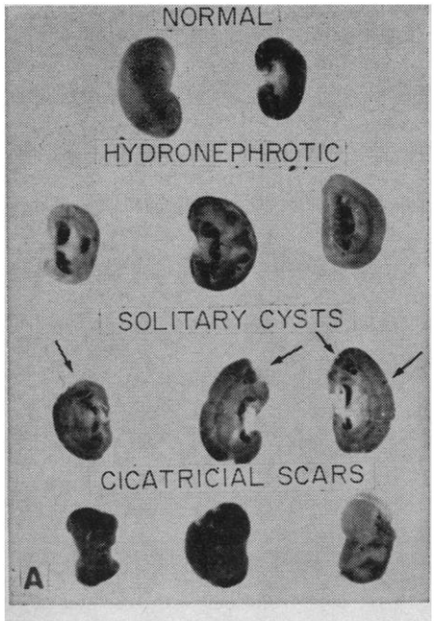
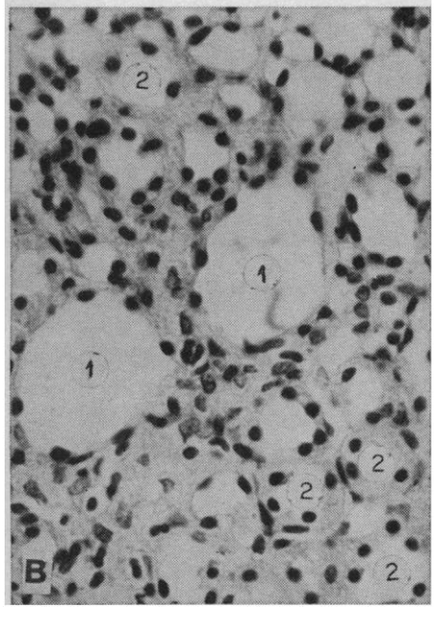


Fig. 1. Pedigree chart of 488 rats showing the dominant inheritance pattern of the kidney disease and its segregation from the recessive mutant characteristic of Gunn rats.





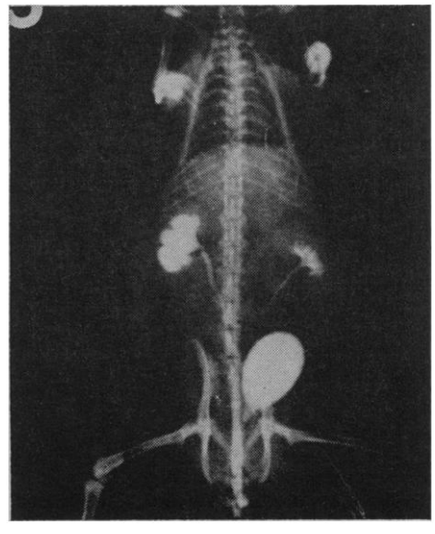


Fig. 2. (A, top left) Macroscopic lesions found in rats with hereditary renal disease. (B, center) One type of microscopic lesion in dilated (1) and normal (2) renal tubules. Periodic acid-Schiff staining × 400.

Fig. 3. (bottom left). Urogram of rat suffering from hereditary renal disease. Advanced hydronephrosis is seen in the right kidney. Normal renal pelvis and ureter are present in the left kidney.

bilirubin at the tips of the papillae (*5*). In our colony of rats this deposition of bilirubin was observed in all jaundiced rats, whether or not hydronephrosis or cysts were present. Inheritable urogenital anomalies have been described in Wistar albino rats by Hain and Robertson (*2*). Different types of renal defects, including congenital hydronephrosis, were observed in a small proportion of the animals they studied. These authors presented evidence that the renal anomalies were inherited but did not define the mode of inheritance, and no attempt was made to establish a colony of rats carrying such abnormalities. Our strain of rats has a clearly defined mode of inheritance and constitutes an experimental model with macroscopic and microscopic lesions very smilar to those observed in humans. This animal model therefore offers a unique opportunity for further studies of the embryologic defects leading to congenital hydronephrosis.

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Agglutinating Specificity for LW Factor in Guinea Pig and Rabbit Anti-Rh Serums

Abstract. *Serums produced in guinea pigs or rabbits inoculated with monkey (rhesus or baboon) or human red cells contain the same high-incidence agglutinating activity found in human anti-LW serums. After one absorption with LW-negative blood cells, anti-LW specificity was observed with stronger reactions on Rh-positive than Rh-negative cells. The 85-percent specificity was obtained after complete absorption with Rh-negative blood.*

The findings reported here show that serums of guinea pigs and rabbits injected with monkey (rhesus or baboon) or human red cells contain the same high-incidence agglutinating activity found in human anti-LW (Landsteiner-Wiener) serums (*1*, *2*). The latter serums react more strongly with Rh-positive than with Rh-negative cells, and not at all with LW-negative cells, which are very rare and consist of two types: namely, those bearing Rh antigens (*1*, *2*) and Rh_{null} bloods lacking all Rh antigens (*3*).

In the earlier studies with animal immune serums, LW-negative cells were not yet described, and hence complete absorption was carried out, as a rule, with random human Rh-negative cells which, however, are LW-positive. Thus the resulting specificity gave 85 percent of positive reactions with human red cells, as first observed by Landsteiner and Wiener (*4*). The positive and negative reactors have been called Rh positive and Rh negative and more specifically D or Rh_o positive or negative. Later the specificity of these animal immune serums was referred to as "anti-D like" but differed from human anti-D in several respects. In the first place the D-like antigen, now known as LW (*1*), was present in Rh-negative cells as shown by their antigenicity in animals and their capacity to yield eluates of the same specificity. Second, the D-like antibody still agglutinated Rh-positive red cells which were fully coated with human incomplete antibody to D (*5*). Third, human anti-LW serums produced by Rh-positive or Rh-negative patients failed to react with selected Rh-positive or Rh-negative individuals who were LW-negative. This was observed in siblings of propositi who produced anti-LW (*1*, *2*). In still another respect, LW antigen differs from human D (Rh_o) since the latter is