The term *nephronophthisis* was first used by Fanconi et al. [1] in 1951 to describe a disease characterized by its occurrence in siblings, a prominent defect in urinary concentrating ability, anemia, and progressive renal failure (in the absence of hematuria, heavy proteinuria, or hypertension) leading to death before puberty. At autopsy, the kidneys were markedly shrunken and had prominent tubulo-interstitial damage. In view of the familial occurrence with a horizontal distribution, and consanguinity in one of the two families, the authors suggested an autosomal recessive inheritance, and named the disease familial juvenile nephronophthisis (FJN). Several reports confirming the distinctive features of the disease have been published first in Europe [2–6], where 39 cases were reviewed in 1963 [6], and then in the U.S.A., where the first case was reported in 1964 [7].

During the same period, a disease characterized clinically by progressive uremia in the absence of major urinary abnormalities, except for polyuria, and characterized pathologically by the presence of medullary cysts was first reported in a child [8] and then in a few adults [9]. In 1961, Strauss [10] gathered 18 patients, most of them from the literature, who presented with renal failure and had medullary cysts. He named this condition medullary cystic disease (MCD). Habib et al. [11] were the first, in 1965, to point to the similarity between MCD and FJN. Two years later, Strauss himself [12], as well as Mongeau et al. [13], accepted the clinical and pathological identity of MCD and FJN. Other authors stressed the coexistence of medullary cysts and of
histological lesions of FJN [14–20]. However, the MCD cases described by Strauss were rarely familial (2/18), and they occurred more frequently in adults than in children.

Although in most of the affected families the history is suggestive of a recessive inheritance, in others a dominant pattern of inheritance appears to apply. Some of these reports are based on the investigation of large kindreds, which were described as having nephronophthisis [21–23], MCD [24–27], or both [13, 14, 17]. The majority of the patients were children, but the disease was occasionally found in adults, some of them in the fourth or fifth decade of life [10, 25–28] or even older [29]. This high degree of heterogeneity made a single entity unlikely. Some authors proposed to keep the term MCD for the cases with a dominant inheritance that occur in adults and the term FJN for the juvenile recessive forms of disease. However, it must be remembered that in the past the two names have been used independently of such criteria, that a limit for age is difficult to delineate, that juvenile and adult forms coexist in the same family with either recessive [16, 30–32] or dominant [13, 17, 21, 22] inheritance, that in many instances the genetic transmission cannot be clearly defined, that the term MCD is misleading because medullary cysts exist also in FJN, and that tubulo-interstitial chronic nephritis exists in many other conditions. Thus, the diagnosis has to be based on an array of clinico-pathologic findings. This is why some authors prefer to speak of the MCD–nephronophthisis complex [33, 34].

When well-defined entities, such as those resulting from an enzymatic defect, may be the result of several genetic defects, the genetic analysis of a disease with such blurred outlines and such poor diagnosis criteria as nephronophthisis is difficult to perform. It seems, however, that a major group of patients can be distinguished in whom the disease is consistent with a recessive mode of inheritance. We will first consider among them those who have the typical form of JN, then some with atypical forms, i.e., forms with unusual age at onset, forms with associated disorders and forms with an apparent dominant mode of inheritance.

NEPHRONOPHTHISIS WITH RECESSIVE MODE OF INHERITANCE

Typical juvenile nephronophthisis

Typical juvenile nephronophthisis (JN) corresponds to the disease described by Fanconi et al. [1]. The condition has long been considered as rare, but it is now generally admitted that its frequency has been underestimated and that it actually represents a major cause of end-stage renal disease (ESRD), at least among children. Nephronophthisis was the primary disease in 10% [34], 22% [35], 32% [36], and 15% (personal series) of the children treated for renal failure. Its prevalence in different countries is impossible to assess. There are only two series [34, 37], besides our own [30], that contain more than 20 patients. In addition to Europe and North America, the disease has been reported in Japan [38], South America [39], Iran [40], Israel [41], and in patients