*Kidney International, Vol. 58 (2000), pp. 925–943*

PERSPECTIVES IN RENAL MEDICINE

# Estimating prevalence in single-gene kidney diseases progressing to renal failure

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**Estimating prevalence in single-gene kidney diseases progressing to renal failure.** Incidence and prevalence, the measures of "frequency," are often confused. While in a nonhereditary situation, the useful parameter is the incidence rate, evaluating the impact of an etiologic factor, it is prevalence that is considered useful in a hereditary disease. Prevalence may concern either the whole population or a fraction of this population, that is, males or females or individuals at a given age, for example, at birth. Pathologic phenotype and morbid genotype prevalences have to be clearly differentiated. In this article, we review the epidemiologic surveys allowing an estimation of the distribution of major single-gene kidney diseases progressing to renal failure in different populations. In order to compare their results, the geographic/ethnic composition of the population, the determination of its size, the choice and mode of calculation of the epidemiologic measure, the definition of the disease and modes of diagnosis, the inclusion of cases, the sources of ascertainment and the possible causes of underascertainment, and the period of time during which events were counted should be analyzed accurately. Although their impact in terms of morbidity, hospitalizations, mortality, and cost to society is high, this review shows that information on the prevalence of single-gene kidney diseases is far from complete. To date, the data essentially apply to large populations of European origin. A part of the variation among prevalence data may be due to methodological differences. Not representative are the small populations in which some rare diseases, especially recessive, are found with a high prevalence.

The last decade has shown increasing awareness of the problems encountered in diagnosis of single-gene kidney diseases. The use of molecular genetics in these diseases has culminated in the mapping of most genes (Table 1). In addition, DNA analysis disclosed locus heterogeneity in a large number of them, meaning that mutations in either of two (or three) separately located genes result in the same phenotype. In contrast with these precise data, it became apparent that our information on the frequency of single-gene kidney diseases was far from complete. Individually, most of them, except for autosomal dominant polycystic kidney disease (ADPKD), are rare. However, taken as a whole, their impact in terms of morbidity, hospitalizations, mortality, and cost to society is high. The purpose of this article is to report and discuss the descriptive epidemiologic studies measuring the distribution of major single-gene kidney diseases progressing to end-stage renal disease (ESRD). These surveys may also allow an estimation of the frequency of new mutations produced to replace the genes lost by natural selection, or the mutation rate.

**Key words:** prevalence, polycystic kidney disease, Alport syndrome, nail-patella syndrome, Finnish-type nephrotic syndrome, nephronophtisis, Bardet-Biedl syndrome, cystinosis, primary hyperoxaluria type 1, Fabry disease, von Hippel-Lindau disease, tuberous sclerosis.

Received for publication July 12, 1999
and in revised form April 7, 2000
Accepted for publication April 14, 2000



## MEASURES OF DISEASE FREQUENCY

### The basic measures

To characterize the importance of a gene, of a genotype, or of a phenotype (normal or pathologic) in a given population, geneticists often use the term "frequency." This term is imprecise, however, when considering hereditary diseases. In this situation, in order to quantitate morbidity, it is necessary to use measures traditionally used by epidemiologists, that is, incidence and prevalence [1]. Although these measures are defined differently, are estimated differently, have different units, and have different ranges of possible values, they are often confused [2]. The terms used in this review refer to the definitions given below, even if the authors used a different term.

Even today, ambiguities persist concerning the concept of incidence and its measures [3]. The incidence rate in a given population measures the number of new (or incident) cases of a disease occurring during a specific period. Three components are required: *N*, the number of individuals at risk in the population; d, the number

**Table 1.** Major single-gene renal diseases progressing to end-stage renal disease

| | Inheritance | Gene | Chromosome |
|---|---|---|---|
| Structural disorders of the kidney | | | |
| Autosomal dominant polycystic kidney disease (ADPKD) | AD | *PKD1* | 16p |
| | AD | *PDK2* | 4q |
| | AD | third gene? | — |
| Autosomal recessive polycystic kidney disease (ARPKD) | AR | *PKHD1* | 6p |
| Glomerular disorders | | | |
| Alport syndrome (AS) | XD | *COL4A5* | Xq |
| | AR | *COL4A3* | 2q |
| | AR | *COL4A4* | 2q |
| Nail-patella syndrome (NPS) | AD | *LMX1B* | 9q |
| Congenital nephrotic syndrome of Finnish type (CNF) | AR | *NPHS1* | 19q |
| Tubular and tubulointerstitial disorders | | | |
| Nephronophtisis (NPH1) | AR | *NPHP1* | 2q |
| | AR | *NPHP2* | 9q |
| Bardet-Biedl syndrome (BBS) | AR | *BBS1* | 11q |
| | AR | *BBS2* | 16q |
| | AR | *BBS3* | 3p |
| | AR | *BBS4* | 15q |
| | AR | *BBS5* | 2q |
| Metabolic disorders | | | |
| Cystinosis | AR | *CTNS* | 17p |
| Primary hyperoxaluria type 1 (PH1) | AR | *AGXT* | 2q |
| Fabry disease | XR | *GLA* | Xq |
| Phakomatoses | | | |
| Tuberous sclerosis (TSC) | AD | *TSC1* | 9q |
| | AD | *TSC2* | 16p |
| von Hippel-Lindau disease (VHL) | AD | *VHL* | 3p |

Abbreviations are: AD, autosomal dominant; AR, autosomal recessive; XD, X-linked dominant; XR, X-linked recessive.

of new cases; and t, the observation period during which every individual at risk of the disease is observed. The incidence rate is given by $\frac{d}{Nt}$. If the population is stable and the disease is rare, the denominator (person-years) is the product of the number of years of observation by the size of the population. Another measure of incidence is the risk or probability of developing disease, also termed "cumulative incidence" by some but not all authors. It is equivalent to the number of new cases of disease in a specified period of time divided by the number of individuals at the start of the observation period.

Prevalence measures the proportion of individuals in a population who have the disease of interest either at a specific point or within a period of time. Two components are required: *N*, the number of individuals at risk in a population; and D, the number of individuals with the disease. Prevalence is given by $\frac{D}{N + D}$. It does not differentiate between old and new cases. It is influenced by factors affecting the incidence of the disease and its course, including treatment, survival, and cure.

It is important to outline the differences that exist in the relationship between etiologic factor and disease in nonhereditary diseases (the epidemiologic situation) and in hereditary diseases (the genetic situation) [4]. In the first situation, the etiologic factor (for example, tobacco) and the disease (lung cancer) are different phenomena. The useful parameter is the incidence rate measuring the impact of the etiologic factor. In hereditary diseases, the genotype (for example, mutation in the gene CFTR) cause of the disease, and the phenotype (cystic fibrosis) are two expressions of the same fact, even if the relationship between them is not complete in case of incomplete penetrance. In this situation, incidence refers to the first diagnostic episode in a person's life, that is, conversion of a normal to an abnormal phenotype. Considering such a measure may be interesting in order to study the genetic or environmental factors implicated in the age at onset of the pathologic phenotype, but the main measure is prevalence. Prevalence may concern either the whole population or a fraction of this population, that is, males or females or individuals at a given age, for example, children or newborns. Often treated as an incidence measure, the proportion of birth defects, whether detected at birth or not, is an example of prevalence measure because it depends not only on the incidence of defects at conception or during embryogenesis, but also on the prenatal survival of affected fetuses [1]. By analogy, the proportion of children born with a pathologic phenotype (for example, Down syndrome) or a metabolic abnormality (for example, phenylalanine hydroxylase deficiency) in a population of newborns is considered a prevalence measure. Basically, birth prevalence is measured by the number of children born with the genetic disease in a given population divided by the total number of live births in the corresponding time.

## Estimation of disease prevalence

Estimation of disease prevalence involves the collection of all affected individuals over a specified period in the target population. It requires the continuing cooperation of professionals (experienced and dedicated workers or a small team based in the area, who have considerable tenacity and determination) and often high financial costs. The study design should obey several well-defined and carefully described rules so that reported surveys may be compared. When applied to genetic diseases, the traditional epidemiologic questions must, however, be modified. Ethical problems, mostly linked to the specific question of a genetic disease and differing from one country to another, should be considered from the outset.

*The geographic area must be well defined [5].* It usually corresponds to some administrative or political boundary. The area must be sufficiently large to avoid bias from large kindreds, but sufficiently small to allow complete coverage. Five hundred thousand to 5 million classically represent the outer limits for population size. However, in case of relatively rare conditions, a large population needs to be surveyed. All parts of the area should ideally be covered with equal thoroughness. Hence, access to medical facilities and the health care system have to be evaluated in the whole area. Only living cases resident in the area on the prevalence dates are compared with the total population of the area at the same dates.

*The demographic characterization of the denominator population should be based on official statistics.* The number of individuals at risk is generally estimated through a national census, conducted once every 10 years. This may be a problem in developing countries where censuses are infrequent or where significant undercounting occurs. Moreover, because human populations are dynamic groups with individuals continuously joining or leaving (deaths, births, and migration), intercensal estimates may be wrong. Some countries or regions that are characterized by a stable population with relatively little migration (for example, the department of Cotes d'Armor in France and Wales in the United Kingdom) have been choice locations for epidemiologic surveys.

*Accurate information on the age, sex, and if possible, ethnic characteristics of the population should be available so that appropriate denominators can be used.* Data specific to age (standard-age groups), sex, and ethnic groups may be used. For diseases occurring in childhood, prevalence in the corresponding age group seems preferable to prevalence in the whole population. Because of the severity in males, sex-specific data should be provided in dominant X-linked diseases [for example, Alport syndrome (AS)].

*The study should be continued over a considerable period of time [5].* Three years appears to be a minimum study period, and five years is preferable. It has been shown that a survey, if repeated after an interval, usually produces a significant increase in prevalence.

*The prevalence date should be chosen to be sufficiently remote from the time of the study to allow existing cases to be recognized and diagnosed, but not to have died and been forgotten [5].* This interval, obviously depending on the characteristics of each disease, should be discussed from the outset. In poorly known diseases [for example, Fabry disease or nail-patella syndrome (NPS)], it may take more than five years (or even more) for a diagnosis to be reached.

*To detect index cases, as many separate sources of ascertainment should be used as possible.* Each of the sources (for example, registers, reports from hospitals, clinics, private physicians, family doctors, genetic clinics, biology, radiology and histopathology laboratories, death certificates, and patient associations) may possibly yield information on patients not detected by means of the other sources. Ad hoc registers with regular collection of data constitute the best method of ascertainment [6]. In contrast, other sources are structures that recruit cases without having an epidemiologic vocation. Most widely used are the population of a specific hospital or of a hospital unit or the experience of a number of hospitals, most authors presuming that all patients are admitted to hospitals. Depending on the clinical presentation of the disease, various sources besides nephrology departments (for example, urology departments, ophtalmological clinics, and institutes for the mentally handicapped) may be consulted. Furthermore, some information on the relative prevalence can be derived from the frequency at which specific diagnoses (for example, lysosomal storage diseases and inborn errors of metabolisms) are made by reference laboratories.

When multiple sources of ascertainment are used, the identification of individuals is crucial. It should be remembered that medical files of patients are confidential. In some countries, cross-checking may be forbidden by law, thus introducing sometimes serious limitations to the feasibility of the research.

*Because of the variability of clinical expression of each disorder, diagnostic criteria should be homogeneous throughout the country (problem of numerous investigators) and the period considered.* The phenotypic classification is heterogeneous, being based on the presence of clinical manifestations and/or laboratory tests. Ideally, molecular DNA analysis in patients with minor symptoms or before the disease is clinically obvious would eliminate misclassification. Its application to such studies does not seem feasible. Correctness and firmness of diagnosis have to be evaluated in all patients. This issue is crucial for disorders with incomplete penetrance where the characteristic phenotype may not be expressed at all in some individuals carrying the mutation.

*Causes of underascertainment should not be ignored.* Complete ascertainment can never be proven, but arguments may support the assumption of an optimal sam-

pling of all patients. Failures in reporting and/or underdiagnosis (for example, lack of reporting, incomplete retrieval of hospital and office charts, inability to trace known patients, lack of response to postal inquiries, renal condition omitted from death certificates, patients with multiple problems, often the elderly, usually followed by general physicians, and mild cases missing if only hospitals provide cases) result in underestimation of the prevalence.

Several investigators claimed that any study determining disease frequency should incorporate a formal assessment of undercount [7]. In their opinion, the capture-recapture method, widely used in animal ecology to estimate population size, is a means to obtain an accurate evaluation of the nonascertained cases. Briefly, this approach uses the number of cases found by a primary source and by a secondary source and the number of cases common to both. Using the source overlap information, the total population can be estimated, and 95% percentage confidence intervals can be placed around this estimate [8]. For other authors, the applications of the model are restrictive and, when applied to medical conditions, are not usually met in practice [9]. First, the method requires independent sources for accurate estimates. In human diseases, being on one list is often associated with being on another. Second, there may be a portion of false-positive cases among the subjects identified as having the disease. Calculating a standard deviation for the estimation of missing cases does not solve the problem of underascertainment, and in their opinion, the method cannot replace a direct population survey. As shown by a recent exchange on tuberous sclerosis (TSC), supporters of the capture-recapture method [10] are opposed to supporters of direct population surveys [11].

*Once an index case(s) has been identified, complete families should be carefully evaluated.* Such an intensive search requires sheer effort, and detective work is essential. Secondary symptomatic cases, some previously undiagnosed, others recognized but not previously ascertained by the investigator, may be discovered [5]. As previously mentioned, ethical conduct may be a limitation to the study, since it is necessary to obtain permission from index patients to contact relatives.

Investigators have to decide whether they will determine the frequency of the pathological phenotype or the frequency of the morbid genotype. In the first design, index cases and symptomatic relatives are included. However, in late-onset disorders such as autosomal dominant diseases, many heterozygotes will be symptomless for a part of their lives. As a result, only a proportion will be recognized as affected even though most will develop the disease. Consequently, systematic screening may be proposed to asymptomatic relatives. One may ask whether it is ethical to use screening simply in order to classify them as likely or unlikely to have the disease. In any case, a screening test(s) should be acceptable, cheap, and valid (for example, kidney ultrasonography in ADPKD).

The second design includes nonscreened asymptomatic heterozygotes. According to the expectations of autosomal dominance, the risk of a person with an affected parent, sibling, or child being heterozygous is 50%, and the risk of a person with an affected grandparent being heterozygous is 25%. Asymptomatic heterozygotes will consequently be estimated by counting one half of those with 50% risk and one quarter of those with 25% risk in complete pedigree structures obtained in each family. Such a calculation using crude prior risk percentages results in an overestimation of the number of heterozygotes. Different methods of correction, depending either on age-at-onset distribution or age-related risk, previously established for the disease under study, have been recommended [5].

*Birth prevalence.* Ideally, birth prevalence should be evaluated from population-based newborn surveys or from following a cohort of births in which the genetic disease is ascertained at various ages. Official information on the annual number of newborns is usually provided in each country.

If the disease is not apparent at or shortly after birth, another means is to conduct a retrospective study allowing calculation of the proportion of children with a given disease born each year in a given population. In addition to renal diseases in which onset occurs in infancy [that is, congenital nephrotic syndrome of Finnish type (CNF)], such an indirect measurement appears valuable when onset occurs in early childhood [that is, autosomal recessive polycystic kidney disease (ARPKD), X-linked AS in males, nephronophtisis, cystinosis]. Ascertainment depends not only on the completeness of recognition of the clinical phenotype and reporting, but also on the survival (infants or children might die without the disease having been diagnosed), on the length of the study period (children having not yet presented typical signs are missed), and on possible family departure before apparent onset.

Finally, risk on the one hand and heterozygote frequency on the other hand may be considered equivalent of birth prevalence. When the whole life is considered and if penetrance is complete, estimation of risk allows for an estimation of prevalence in a population of newborns. In the case of incomplete penetrance, this estimation should be corrected. Reduced survival as well as competing causes of death, however, will produce an underestimation. Similarly, heterozygote frequency in a dominant condition may be considered the equivalent of those having the morbid genotype at birth and who are expected to be affected in the future.

*Prevalence in small populations.* Prevalence estimates in small populations must be considered with caution. They may not be representative of the common preva-

lence values. It is well known that rare hereditary diseases, especially recessive, may occasionally be more frequent in small populations (for example, Finns and French Canadians) than elsewhere. In some cases, genealogical studies suggested that the mutation might have been introduced by a small group of related individuals splitting off from existing populations (founder effect) [12]. Conversely, diseases that are otherwise relatively common may be rare, even absent, or about as frequent in these small populations.

## MUTATION RATES

Many mutations reduce the life span or reduce the ability of the person to reproduce or interfere with both. Thus, a mutation with a deleterious effect on the phenotype tends to be selected against. The term "mutation rate" refers to "the probability with which a particular mutational event takes place in a fertilized germ cell per generation" [12]. It is necessary to study disorders that occur relatively frequently to find a sufficient number of cases to provide the basis for a reasonable estimate. Underascertainment of affected individuals leads to underestimation of mutation rate.

Only applicable to autosomal dominant traits, direct calculation of the mutation rate can be made after evaluation of the family history and verification that the disease was not present in either parent [1]. Classically, the mutation rate $\mu$ is given by the number of children born with a given genetic disease whose parents do not transmit the disease divided by 2 $N$, $N$ being the number of live births during the study period, and the division by 2 being necessary because the number of gametes is double the number of individuals. However, most dominant diseases are not discovered at birth, and only prevalence data obtained later in life are available. Estimation of mutation rate will, of course, depend on survival of affected individuals.

The indirect approach may be applied to various modes of inheritance, and formulas have been derived for each mode [1]. The principle is that there is a genetic equilibrium between mutation and selection in human populations. Selection can be measured in terms of fitness, symbolized as f, where $f = 1$ implies no impairment in fertility relative to the general population, and $f = 0$ corresponds to complete infertility. In autosomal dominant diseases, the formula is $\mu = \frac{1}{2}(1 - f)p$, where p is the birth prevalence. A useful approximation for f can be obtained by comparing reproduction of patients with that of their unaffected sibs. Another way is to determine the number of children in a random age group of the population with follow-up to the end of their reproductive period in comparison with patients.

## AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Autosomal dominant polycystic kidney disease is characterized by progressive renal cyst formation and expansion leading to ESRD. Other manifestations include the presence of cysts in other organs (liver, pancreas), heart valve defects, and an increased frequency of intracranial aneurysms. Two different loci are known to cause ADPKD, PKD1, and PKD2. There is still an unmapped locus. In European families, linkage studies have estimated that PKD1 accounts for 86% of the disease and PKD2 for most of the remaining cases [13]. The proportion of PKD1 families appears almost identical in Japan [14].

Autosomal dominant polycystic kidney disease is considered the most common single-gene disorder that results in renal failure. ADPKD represented 2.6 and 2.9% of all incident cases of treated ESRD during the years 1992 to 1996 in the United States [15] and during the years 1986 to 1994 in Japan, respectively [16]. If we consider that ADPKD represents the near totality of patients classified as having "cystic kidney diseases" in the United States, the adjusted incidence rate of ESRD patients with ADPKD was approximately 7 per million population per year (for the year 1996) and the adjusted point prevalence approximately 50 per million population (on December 31, 1996) [15]. Distribution was not uniform among all ethnic groups; however, 3.4% of the ESRD patients were Caucasian, 2.0% Asian, 1.2% Native American, and 1.1% African American. In Japan, the incidence of ESRD patients with ADPKD was 4.8 per million population per year (for the year 1995) [16].

However, many patients never reach ESRD, and many reach it only late in life. Although case inclusion differed, two studies on age-related ESRD carried out in Canada [17] and in France [18] showed that prognosis was much better than the previous clinical reports suggested. To avoid an ascertainment bias, Canadian authors excluded index cases and based their analysis on family members with cysts on ultrasonography. They showed that 25% had ESRD by the age of 47 years, 50% by the age of 59, and 75% by the age 70. The French authors, who included both probands and relatives with positive ultrasonography, concluded that 22% had reached ESRD by the age of 50 years, 42% by the age of 58, and 72% by the age of 73 years. Neither of these studies showed any difference between males and females. In contrast, the Japanese survey showed a significant difference in mean age at initiation of dialysis between females ($54.5 \pm 10.7$ years) and males ($52.3 \pm 11.7$) [14].

Phenotypic variability between families and within families is obvious. Some of the variability between families is due to the gene. Compared with PKD1 patients in a multicenter analysis, PKD2 patients presented with symptoms later in life, lived longer, had a lower risk of

progressing to renal failure, and had fewer complications. The median age at death or ESRD was 53.0 years (95% CI, 51.2 to 54.8) in individuals with PKD1 and 69.1 years (95% CI, 66.9 to 71.3) in those with PKD2 [19]. Consequently, with PKD2 being a less severe disease, its relative frequency may be underestimated.

After the 1956 landmark study in Denmark by Dalgaard [20], which was the sole source of data on "frequency" over a large number of years, surveys were conducted in the United States [21], the United Kingdom [22], France [23], the Seychelles [24], and Japan [16]. These studies, carried out at different periods, largely differed in criteria for ADPKD diagnosis, sources of ascertainment, and case inclusion. It should be noted that in all, missing patients, especially those with less severe disease (probably the PKD2 patients) and a possible failure to detect isolated cases, may be causes of incomplete ascertainment. They also differed in the choice of epidemiologic measure since prevalence was estimated in the four last studies [16, 22–24], but it was risk that was evaluated in Denmark [20], whereas both incidence rates [21] and risk [25] were evaluated in the United States.

## Estimation of risk

Dalgaard's estimation of risk is invariably quoted as an estimation of prevalence in the general population. In fact, as previously mentioned, such a risk allows the estimation of birth prevalence of heterozygotes [4]. Nevertheless, the use of Dalgaard's risk as ADPKD birth prevalence, without considering the competing causes of death in the first part of the 20th century and the possibility of ADPKD being undiagnosed, should be considered with caution.

Judging that a certain number of cases might not be diagnosed, Dalgaard chose to estimate "the risk of being ill from a certain disease during the course of one's life" [20]. He established a list for all "fresh" cases of typical bilateral polycystic kidneys that appeared in Copenhagen during the periods 1920 to 1935 and 1935 to 1953 (Table 2). Only probands were included in the calculation. Their number diagnosed in each age group (15 to 19, 20 to 24, 25 to 29, . . . 75 to 79 years) was compared with population figures, according to age and sex. The five-year incidences, that is, the number of cases arising per 100,000 of the general population in the course of five years, were calculated. Summing incidences in each sex led to establishment of risk curves. That curves for the period prior to 1935 were below those after 1935 was explained by improvement in social conditions leading to an increase in hospital admissions and improved diagnostic methods. From data obtained in the period 1935 through 1953, Dalgaard concluded the following: "*The actual risk of having polycystic disease of the kidneys before the age of 80 is estimated as being hardly 1 per thousand. This estimation is a minimum figure, and must*

**Table 2.** Description of studies on estimation of risk in ADPKD

| Disease [Reference] | Country, region | Sources of ascertainment | Risk period | Age of population | Size of Population | *N* of new affected | Risk per 100,000 |
|---|---|---|---|---|---|---|---|
| ADPKD [20] | Denmark, Copenhagen | Medical, surgical and Roentgen departments in Copenhagen (13 hospitals and one private clinic)<br>Autopsy records from hospitals<br>Death certificates from the Office of Medical Statistics<br>Institute of Human Genetics | 1935–1953 | >15 years | Women 403,600<br>Men 331,900 | 91[a]<br>77 | 82.3 ± 10.1<br>89.7 ± 12.7 |
| ADPKD [21, 25] | United States, Olmsted County, Minnesota | Mayo Clinic and Olmsted Medical Group | 1935–1980 | Whole | 92,000 | 40[b] (rate A)<br>56[c] (rate B)<br>72[d] (rate C) | 100[e]<br>—<br>250[e] |

[a] The authors included probands only. Living relatives found to have bilateral polycystic kidneys on systematic urography were not included in the calculation
[b] Probands plus relatives found to have bilateral cystic kidney changes on radiographic findings: ultrasonography, surgical exploration (incidence rate A per 100,000 person-years: 1.40)
[c] Plus cases discovered at autopsy, the date of death used as the date of the first episode (incidence rate B:1.96)
[d] Plus additional cases if all deaths come to autopsy (incidence rate C:2.52)
[e] Approximately

*be regarded as an approximation.*" There was no significant difference between females and males.

A different study was conducted in Olmsted County in order to estimate incidence rates in the years 1935 to 1980 (Table 3). [21] The survey was based on the Rochester Epidemiology Program Project that supports population-based studies of disease unique in the United States, if not in the world [26]. Olmsted County is isolated from other urban centers, the population relatively stable, and medical records combining inpatient and outpatient data assured the identification of almost all local residents in whom a given disorder has been diagnosed. During the period studied, more than 50% of all deaths were autopsied. According to the mode of diagnosis, three incidence rates were defined. The calculation of rate A was based on the number of symptomatic cases diagnosed during life as well as those detected during family screening. For the calculation of rate B, the authors added the patients in whom diagnosis was made at autopsy. Incidence rate C included an additional number of cases that would have been found if all deaths of Olmsted County residents had been autopsied. Comparing rates A and C, the authors suggested that only about half of the patients were clinically diagnosed during life. Using these data, Torres, Holley, and Offord were able to calculate the morbid risk [25]. By the age of 80, the minimum risk (based on data used in calculation of rate A) was approximately 1 per 1000, and the maximum risk (based on data used for calculation of rate C) increased to 2.5 per 1000 (Table 2). As compared with curves for the Copenhagen population, the Olmsted County curves indicated an earlier diagnosis of the disease.

## Morbid genotype prevalence

Although their sources of ascertainment differed, two surveys, one carried out in South and Mid-Wales in the United Kingdom [22] and the second in a French region, the department of Cotes d'Armor in Brittany [23], were both conducted to measure the prevalence of symptomatic and asymptomatic heterozygotes (Table 3). In Wales, heterozygote frequency was 41 per 100,000 (or 1 per 2459), 2.8 times the pathologic phenotype prevalence. In Brittany, heterozygote frequency was 90 per 100,000 (or 1 per 1111), 2.2 times the pathologic phenotype prevalence. On the one hand, both evaluations using crude prior risk resulted in an overestimation of the number of heterozygotes. On the other hand, ascertainment was unlikely to be complete. The French study was single hospital based. In contrast, in Wales, index patients were ascertained through a register, but most presented with renal failure. Families with a benign prognosis may have been missed.

## Pathologic phenotype prevalence

Prevalence was estimated in the Seychelles, an island in the Indian Ocean, where 65% of the population is of

**Table 3.** Description of studies on prevalence of the morbid genotype in ADPKD and VHL

| Disease [Reference] | Country, region | Sources of ascertainment | Prevalence day | Age of population | Size of population | *N* affected | Point prevalence per 100,000 |
|---|---|---|---|---|---|---|---|
| ADPKD [22] | United Kingdom, South and Mid-Wales | Local genetic register | 31/12/1989 | Whole | 2,100,000 | 854[a] | 41 (1/2,459) |
| ADPKD [23] | France, Department of Cotes d'Armor | Nephrology unit (Saint Brieuc Hospital) | 1/12/1993 (1988–1993) | Whole | 410,644 | 371[b] | 90 (1/1,110) |
| | | | | 20–39 years | NS | NS | 35 |
| | | | | 40–59 years | NS | NS | 92 |
| | | | | 60–79 years | NS | NS | 73 |
| VHL [94] | England, East Anglia | Specialists in genetics, nephrology, neurology, neurosurgery, ophthalmology and urology | 1/7/1990 | Whole | 2,034,000 | 38.5[c] | 1.89 (1/53,000) |
| | | | | 25–49 years | NS | NS | 2.73 (1/36,000) |
| VHL [95] | England, North West | Regional registry for VHL | 30/11/1994 | Whole | 4,030,800 | 47.4[d] | 1.18 (1/85,000) |
| | | Genetic center (Manchester) | | 25–49 years | 1,428,471 | 31.4 | 2.20 (1/45,500) |

[a] The authors combined (1) probands ($N_1 = 242$); (2) asymptomatic relatives with cysts in both kidneys and at least two or more cysts in one kidney on ultrasonography ($N_2 = 61$); (3) asymptomatic relatives with a 50% prior risk ($N_4 = 867$), from whom relatives with negative scan and aged over 30 years were withdrawn ($N_3 = 92$); (4) asymptomatic relatives with a 25% prior risk ($N_5 = 657$). Total: $N_1 + N_2 + \frac{N_3 - N_4}{2} + \frac{N_5}{4} = 854$

[b] The authors combined (1) probands aged 24–80 years ($N_1 = 24$); (2) asymptomatic relatives aged over 20 with three cysts in each kidney on ultrasonography ($N_2 = 44$); (3) asymptomatic relatives with a 50% prior risk ($N_3 = 232$); (4) asymptomatic relatives with a 25% prior risk ($N_4 = 347$). Total = $N_1 + N_2 + \frac{N_3}{2} + \frac{N_4}{4} = 371$

[c] The authors combined (1) patients ($N_1 = 24$); (2) asymptomatic relatives with a 50% prior risk, their number being corrected by age-related risk curves ($N_2 = 9.4$); (3) isolated cases below 25 years and not yet diagnosed, their number being deducted from the total number of isolated cases and the size population in the age group below 25 years ($N_3 = 5.1$). Total = $N_1 + N_2 + N_3 = 38.5$

[d] The authors combined (1) patients ($N_1 = 26$); (2) asymptomatic relatives with a 50% prior risk, their number being corrected by age-related risk curves ($N_2 = 17.6$); (3) isolated cases below 25 and not yet diagnosed, their number being derived from the number of isolated cases and the size population in this age group ($N_3 = 3.8$). Total = $N_1 + N_2 + N_3 = 47.4$

African descent and 30% of Caucasian or mixed descent [24] (Table 4). The study included not only index cases, but also asymptomatic relatives found to have cysts on ultrasonography. Not all accepted screening, thus leading to a possible underascertainment. All patients but one were Caucasian, so that the prevalence in the African and Caucasian populations were 2 and 184 per 100,000 (or 1 per 544), respectively, increasing to 6 and 236 per 100,000 in the 25 to 39 age group. According to the authors, a race differential detection of ADPKD is unlikely since access to medical care is available and free of charge to all inhabitants. The high prevalence in the Caucasian population suggested a founder effect. It was hypothesized that the ADPKD gene(s) might have been introduced to the island by one or more Caucasian individuals among the few initial settlers and was conserved in the Caucasian community, as interracial marriage was long uncommon.

The nationwide Japanese survey was conducted differently [16]. Using the 1994 data obtained in departments of nephrology randomly selected by a stratified sampling method from all hospitals, the number of ADPKD patients without renal replacement therapy (RRT) was estimated to be 10,000 (CI 8200 to 11,900). Adding the 4594 patients on dialysis gave a prevalence of 11.7 (CI 10.2 to 13.2) per 100,000. Prevalence increased with age, reaching 26.1 per 100,000 in the 55 to 59 years age group. The authors, assuming that there were patients not yet diagnosed, adopted this high prevalence as that of patients below 55 years and consequently estimated the total number of ADPKD individuals to 31,000. This gave a prevalence of 25 per 100,000 (or 1 to 4033). This approach, based only on patients who were seen in Japanese hospitals during a single year, likely underestimates the true prevalence of ADPKD in Japan.

### Mutation rates

The only study on mutation rate in ADPKD was provided by Dalgaard, who judged it necessary to rely on an indirect method [20]. Fitness was estimated at 0.77 to 0.87 by comparing the number of births in Copenhagen and the number of children born to patients, while taking into account age at death and the year of birth. The mutation rate was 6.5 to $12 \times 10^{-5}$ per gene per generation. Specific surveys are now needed to assess the mutation rate corresponding to each of the implicated *PKD1* and *PKD2* genes.

## AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

In ARPKD, the histologic changes are specific with dilated collecting ducts and dysgenesis of the portal triad. Contrasting with this clear-cut anatomical definition, the disease remains difficult to define from a clinical point of view. There is considerable variability in the degree of involvement of the kidney and liver, with a clinical spectrum ranging from infants not surviving the first months of life to mildly affected adults. Although extremely high in a Finnish study, the proportion of the lethal neonatal form is not known [27]. It should be noted that ARPKD does not belong to the group of recessive diseases over-represented in Finland. There is, however, no evidence of genetic heterogeneity. Outcome of patients who survive the first month of life is variable, but has become better than previously reported. Life-table analysis reveals an actuarial renal survival of 86% at one year and of 67% at 15 years [28]. ARPKD accounted for 1.5% of children who started RRT before the age of 15 years between 1987 and 1991 in Europe [29], and for 0.6% of incident cases of treated ESRD before the age of 20 in the United States in the years 1992 to 1996 [30]. The distribution among different ethnic groups is not known, but there were no black ARPKD patients in the ESRD registry in the United States.

The prevalence of the disease remains unknown. The lack of surveys is explained by the confused terminology of cystic abnormalities, the highly variable clinical spectrum, and the difficulties in differentiating ARPKD and ADPKD in children [27]. The estimate of birth prevalence that is widely used was given in 1984 by Zerres, Völpel, and Weiss [31]. Combining data from the United States provided by Potter [32] in 1972, from the Hungarian Congenital Malformation Register for the years 1970 through 1976 [33], and from the pediatric autopsy files of the Children's Hospital, University of Helsinki (Finland) for the years 1974 through 1978 [34], they noted the following: "*Potter (1972) observed two cases born in the Chicago Lying-Hospital during a period in which there were about 110,000 live births. The prevalence of cystic kidneys (type I and II)* [note: type I ARPKD; type II renal dysplasia] *was 0.11/1000 total births in Hungary between 1972 and 1976 [Rutkai and Czeizel 1982]. Mir et al (1983) found about 50% type II and about 10% type I kidneys among their renal cysts in pediatric autopsy material. Combined data correspond with Potter's observation. Because of milder manifestations of type I kidneys an overall incidence of about 1:40,000 may be a useful rough estimate.*" More recently, rectifying their conclusion, they estimated that a birth prevalence of 0.5 per 10,000 live births (1 out of 20,000) should be used [35].

## ALPORT SYNDROME

Alport syndrome (AS) is characterized by hematuria and progressive renal failure, associated with sensorineural hearing loss, sometimes ocular anomalies (anterior lenticonus and perimacular flecks), rarely with leiomyomatosis of the esophagus and tracheobronchial tree. Ul-

**Table 4.** Description of studies on estimation of prevalence of pathologic phenotype in ADPKD, BBS, PH1, TSC and VHL

| Disease [Reference] | Country, region | Sources of ascertainment | Prevalence day or years | Age of population | Size of population | *N* living affected | Prevalence per 100,000 |
|---|---|---|---|---|---|---|---|
| ADPKD [24] | The Seychelles | Physicians, surgeons, pediatricians, radiologists and pathologists | 1/1993–1/1995 | Whole | 74,331 | 42[a] | 57[b] (1/544) |
| | | | | | Caucasian 22,299 | 41 | 184[b] |
| | | | | | African 48,315 | 1 | 2.1[b] |
| | | | | 25–39 years | Caucasian 7,644 | 18 | 236[b] |
| | | | | | African 16,563 | 1 | 6.0[b] |
| BBS [54] | Switzerland | Swiss records for tapeto-retinal degeneration of the Medical Genetic Institute (Geneva)<br>Ophthalmological and pediatric university and cantonal clinics<br>Author's collection (secondary cases) | 11/1964–5/1966 | Whole | 5,900,000 | 37 | 0.69 (1/160,000) |
| BBS [55] | Canada, Newfoundland | Registry of the Canadian National Institute of the Blind<br>Ocular Genetics Clinic<br>Hospitals | ?–1986 | Whole | NS | 32 | 5.71 (1/17,500) |
| BBS [57, 58] | Kuwait | Medical Genetic Center and genetic clinics | 1979–1989 | Whole | 1,300,000 | 36 | 2.78 (1/36,000) |
| | | | | Bedouins | NS | 24 | 7.40 (1/13,500) |
| PH1 [74] | France | Pediatric and adult nephrologists | 1988–1992 | Whole | 56,740,000 | NS | 0.11[c] |
| | | | | 0–14 years | NS | NS | 0.19 |
| | | | | 15–49 years | NS | NS | 0.12 |
| | | | | >50 years | NS | NS | 0.02 |
| PH1 [71] | Switzerland | Pediatric and adult nephrologists | 6/1994 | Whole | 7,038,000 | 18 | 0.26 (1/390,000) |
| TSC [87] | United Kingdom, Oxford region | Department of Medical Genetics (Oxford)<br>Tuberous Sclerosis Association<br>Consultants in pediatrics, dermatology, neurology, neurosurgery, neuropathology, mental handicaps, child psychiatry, ophthalmology, renal medicine<br>Files of the 1968 study | 31/8/1982 | Whole | 2,328,100 | 68 | 2.9 (1/34,200) |
| | | | | <1 years | 32,100 | 2 | 6.2 (1/16,100) |
| | | | | 1–4 years | 122,200 | 8 | 6.5 (1/15,300) |
| | | | | 5–14 years | 349,800 | 19 | 5.4 (1/18,400) |
| | | | | 15–29 years | 551,600 | 20 | 3.6 (1/27,600) |
| | | | | 30–44 years | 491,000 | 5 | 1.0 (1/35,100) |
| | | | | 45–64 years | 487,600 | 5 | 1.0 (1/97,500) |
| | | | | >65 years | 293,800 | 0 | — |
| TSC [82] | United Kingdom, West of Scotland | Regional Genetic Service<br>Unit of Pediatric Neurology (Royal Hospital in Glasgow)<br>Consultants in pediatrics, neurology, dermatology, mental handicap | 1/6/1986 | Global | 2,763,000 | 101 | 3.7 (1/27,000) |
| | | | | <10 years | NS | NS | 8.3 (1/12,000) |
| TSC [88, 89] | United Kingdom, South of England | Pediatricians, neurologists, ophthalmologists, dermatologists, cardiologists, nephrologists, urologists, neurosurgeons, physicians in learning disorders<br>Major regional hospitals<br>Genetic department (Southampton General Hospital and Bristol Hospital for Sick Children)<br>Tuberous Sclerosis Association<br>Histopathology, neuropathology, and neuroradiology departments (major hospitals) | 31/8/1986 | Global | 3,400,000 | 131 | 3.9 (1/26,500) |
| TSC [91] | Sweden, Western region | Pediatricians, child and adolescent psychiatrists and radiologists, child neurologists, physicians in developmental medicine, "habilitation," and mental retardation services, dermatologists, clinical geneticists, audiologists, ophthalmologists, cardiologists, and clinical pathologists | 31/12/1990 | <20 years | 413,084 | 32 | 7.74 (1/12,900) |
| | | | | <5 years | NS | 6 | 5.33 |
| | | | | 6–10 years | NS | 4 | 4.21 |
| | | | | 11–15 years | NS | 14 | 14.7 (1/16,800) |
| | | | | 15–20 years | NS | 8 | 7.23 |
| TSC [90] | Japan, San-In district | Division of Child Neurology and Neurology (Institute of Neurological Science)<br>Departments of pediatrics, dermatology and urology (Tottori University Hospital)<br>Pediatricians, psychiatrists, neurologists and dermatologists (hospitals in Shimane and Tottori prefectures)<br>Institutions for retarded children and adults | 10/1979 | Global | 1,380,000 | 44 | 3.2 (1/31,000) |
| VHL [93] | Germany, District of Freiburg | Freiburg University hospital | 30/6/1989 | Global | 1,908,609 | 49[d] | 2.57 (1/38,951) |

[a] The authors combined (1) probands; (2) asymptomatic first degree relatives with positive ultrasonography (two renal cysts, uni- or bilateral in individuals less than 30 years, two cysts in each kidney in those aged 30–59 and four cysts in each kidney in those aged 60 years and above); one third of them declined investigation

[b] 95% confidence interval 57 (CI 41–76), 184 (41–76), 2.1 (0–11), 236 (140–372), 6.0 (0–33)

[c] 95% confidence interval 0.1 (0.78–1.32)

[d] The authors combined (1) probands with symptomatic angiomatosis retina or hemangioblastoma of the central nervous system ($N_1$ not specified); (2) asymptomatic relatives assessed by a physical, neurological and opthalmological examination, ultrasonography of the abdomen and 24-hour catecholamine assay ($N_2$ not specified). Total = $N_1 + N_2 = 49$

trastructural alterations of the glomerular basement membrane are characteristic. AS, now understood as a consequence of structural abnormalities in type IV collagen, the major component of basement membranes, is genetically heterogeneous. In 85% of the families, the disease is transmitted in an X-linked dominant pattern. Hematuria generally occurs at an average of 3.5 years in affected males. ESRD develops in all affected males and more rarely in affected females. The rate of progression of renal failure shows interfamily variability, that is, families in which the mean age at ESRD in males is less than or greater than age 30. Conversely, in 15% of the families, the disease is transmitted as an autosomal recessive trait. Both young males and females progress to ESRD.

In Europe, AS accounted for 1.5% of children who started RRT [29]. In the 1996 U.S. Renal Data System report, AS represented 0.3% (0.4% male and 0.2% female) of the incident cases of treated ESRD for the years 1989 through 1993 [36]. The great majority of patients were under 20 years of age. Most were white, but black, Asian, and Native American patients were reported.

The long-lasting controversy and confusion over the identification of AS patients were due to imprecise diagnostic criteria, wide phenotypic expression, and different modes of transmission. The estimation of prevalence commonly used was based on clinical experience, not on an epidemiologic survey. Following the observation of a large Utah kindred, Hasstedt and Atkin wrote the following: "*The disease frequency was fixed at 1/5000 for all analyses. This number was a rough estimate of our observation of about 300 known cases in Utah and southern Idaho, with a population of about 1.5 million*" [37]. They subsequently considered that it was the unusual extent of the studies, and not a founder effect, that could explain this high frequency [38].

### Birth prevalence

From familial data on index patients diagnosed as having AS in Finland in the years 1990 through 1994, Finnish authors estimated that birth prevalence should be 0.2 per 10,000 live births (1 out of 53,000; Table 5) [39]. Prevalence in males was not given. As mentioned by the authors, not all families were compatible with X-linked inheritance. Family studies were not complete. Index patients may have been missed, and material was biased toward the more severely affected, since heterozygous females with mild disease in the pedigrees may have been missed.

## NAIL-PATELLA SYNDROME

Nail-patella syndrome (NPS), or hereditary osteo-onycho dysplasia, is an autosomal dominant disorder defined by the association of nail dysplasia, bone abnormalities (absent or hypoplastic patellae, exostoses of the ilia, dysplasia of the elbows), and extraosseous abnormalities, including nephropathy and glaucoma. Interfamily or intrafamily heterogeneity is remarkable, complicating the identification of mildly affected individuals. There is, however, no evidence of genetic heterogeneity. NPS has been described mainly in Caucasians, but also in Asians, in patients from India and the middle East. Only a few were Africans [40].

Renal involvement represents the most serious complication. From combined data of the literature, it appears that glomerular abnormalities (proteinuria) were present in 62% of the cases and that 15% of the patients developed ESRD [40]. However, clinical renal involvement is neither found in all affected families nor in all affected members within families. The presence of collagen fibrils within the glomerular basement membrane is considered pathognomonic and may be detected in patients without proteinuria. This finding highlights the probable underestimation of renal involvement when renal biopsy is not done.

In the absence of epidemiologic surveys, the estimate of prevalence currently used was given by Renwick and Izatt in 1965 [41]. They noted the following: "*There are approximately 255 living patients with the nail-patella syndrome known to us in the United Kingdom, which in the relevant years, 1954-1963, had a mean population size of about 52 million. The count of living affected members was made in a particular way for each pedigree and the fact that this was not the same year for each pedigree produces confusion only in so far as the total national population has increased slightly over the ten-year period. We can therefore confidently state that the prevalence of the syndrome is more than 5 per million.*" Because of the possibility of double ascertainment, the authors modified this estimate: "*Thus, a prevalence figure of five per million can be regarded as very much a lower limit and the true figure is estimated to be about 22 per million, by the rather crude approach of fitting a Poisson distribution to the number of pedigrees ascertained twice (2) and once (18) in order to make a rough estimate of the number of U.K. pedigrees not ascertained at all.*"

## CONGENITAL NEPHROTIC SYNDROME OF THE FINNISH TYPE

Since the 1950s, congenital nephrosis has raised active interest among Finnish pediatricians because it has proved to be exceptionally common in Finns and very rare elsewhere. Attention was focused on a particular group of neonates and infants who had progressive edema and massive proteinuria, showed no response to the standard treatment of nephrotic syndrome, and died early, most of them by the age of two years. The only life-saving treatment is conservative management and renal trans-

**Table 5.** Description of studies on birth prevalence in AS, CNF, NPH1, and cystinosis

| Disease [Reference] | County, region | Sources of ascertainment | Birth prevalence *years* | | *N* livebirths | *N* affected | Birth prevalence per 10,000 livebirths |
|---|---|---|---|---|---|---|---|
| AS [39] | Finland | Nephrologists, internists, pediatric nephrologists, pediatricians (5 university and 16 regional hospitals)<br>Departments of medical genetics<br>Kidney transplantation registry | 1976–1993 | | NS | 22 | 0.2 (1/53,000) |
| CNF [45] | Finland | National list of all cases<br>Death certificates (Statistical Office) | 1965–1973 | | 614,932 | 75 | 1.2 (1/8,200) |
| NPH1 [50] | Finland | Finnish Kidney Transplantation Register<br>Nephrologists, pediatric nephrologists, pediatricians (5 university and 16 regional hospitals)<br>Register of patients <16 years with chronic renal diseases | 1963–1982 | | NS | NS | 0.13 (1/80,000) |
| Cystinosis [64] | France | 176 departments of pediatrics | 1959–1972 | France, except Brittany | 11,425,404 | 35 | 0.03 (1/326,400) |
| | | Hemodialysis centers | | Brittany | 440,458 | 17 | 0.4 (1/25,900) |
| Cystinosis [66] | West Germany | Nephrologic centers | 1960–1979 | | 15,423,898 | 86 | 0.06 (1/179,000) |
| Cystinosis [67] | Denmark | All pediatric departments<br>Medical departments with attached pediatric ward | 1/1/1962–31/12/1971 | | 791,307 | 7 | 0.09 (1/115,000) |
| Cystinosis [68] | Canada, Saguenay-Lac-St-Jean, Quebec | Neuromuscular, cystic fibrosis, pediatrics, and hematology clinics in Chicoutimi Hospital<br>Quebec Medical Genetic Network<br>Lipid diseases department in Laval University Hospital<br>Clinical Research Institute in Montreal<br>Biochemistry department in Sherbrook University<br>Department of Genetics in St Justine Hospital | 1975–1986 | | NS | NS | 0.16 (1/6,237) |
| Cystinosis [60] | France (including Overseas Territories) | Pediatric and adult nephrologists<br>Laboratories in charge of leukocyte cystine assessment<br>List of patients under cysteamine bitartrate capsules | 1972–1994 | | NS | NS | 0.06 (1/167,364) |

plantation at the age of one or two years following bilateral nephrectomy.

About 30 single-gene diseases, most autosomal recessive, have been found to be particularly frequent in the Finnish population and were termed "Finnish Heritage of Disease" [42]. The first to be recognized was CNF. The small number of original ancestors, the location between Russia and Sweden with differing heritage and language, the geographic factors acting as barriers and favoring genetic isolates, the low increase of the population, and the continuing isolation of groups of settlers characterize Finland. The high prevalence of autosomal recessive diseases is due to the chance inclusion or occurrence of one mutation in the small founding population, followed by enrichment through genetic drift in the population that expanded while isolated [43]. CNF is not unique to the Finnish population. Most other cases were reported among Caucasians, but also among blacks, Japanese, American Indians, Tunisians, and Maoris. The same gene seems to be affected in Finnish and non-Finnish families. Mutations of the NPHS1 gene have been observed in non-Finnish patients from Europe, North America, and North Africa [44].

### Birth prevalence

Since the disease was first defined in Finland, a list of all cases has been kept in Helsinki. In 1965, Norio estimated birth prevalence to 1 per 10,000 live births and insisted on the variations in prevalence among different Finnish regions [42]. In the 1976 nationwide survey [45], birth prevalence was estimated at 1.2 per 10,000 live births (or 1 out of 8200; Table 5). Since some infants might die during the first days of life without CNF having been diagnosed, birth prevalence may be underestimated. In East Finland where prevalence was known to be high, prenatal screening (based on a high αfetoprotein concentration in amniotic fluid) was offered to women [46]. If all births had occurred, the birth prevalence would have been 4.2 per 10,000 live births. As a result of the screening and pregnancy termination, it fell to 0.9 per 10,000 live births.

CNF was found to be frequent in a subgroup of the Old Order Mennonites known as the Groffdale (the more conservative group) [47]. Ancestors immigrated from Switzerland during the 18th century to Lancaster County, Pennsylvania, USA, and no explicit Finnish ancestry is known. Birth prevalence was estimated to be 2 per 10,000 live births during the period 1985 to 1994, 20 times greater than that observed in Finland. Genetic analysis showed that mutation of the *NPHS1* gene is most likely of recent origin, uncovered by inbreeding and amplified by genetic drift.

## JUVENILE NEPHRONOPHTISIS

Juvenile nephronophtisis (NPH1) is an autosomal recessive tubulointerstitial nephritis that is characterized by progressive insidious polyuria caused by reduced urinary concentrating ability preceding an ineluctable decline in renal function. ESRD usually occurs around puberty. Great confusion exists in the literature regarding the definition and characteristics of the disease. This results from: (*1*) the absence of clinical, biological, and histologic criteria, although the extreme thickening of the tubular basement membrane with a "tyre-like" appearance seems for some pathologists characteristic of the disease by its severity and diffusion; (*2*) the clinical heterogeneity caused by the number of extrarenal abnormalities described as associated with NPH1, such as tapeto-retinal degeneration with flat electroretinogram (Leber amaurosis) present in 10 to 15% of the patients and constituting the Senior–Løken syndrome, cerebellar ataxia, liver fibrosis, and cone-shaped epiphyses; and (*3*) the clinical and morphological resemblance to an autosomal dominant form named medullary cystic disease (ADMCKD), differing from recessive NPH1 by its mode of inheritance, its clinical course with development of ESRD mainly in adults, and the lack of extrarenal associations.

NPH1 is genetically heterogeneous. In Europe, the *NPHP1* gene is responsible for approximately 85% of the affected families. In more than 70% of these families, *NPHP1* is at least partly deleted. NPH1 patients with and without the deletion do not show significant difference in the rate of progression to ESRD [48]. There is, however, a subset of families, especially the families with Senior-Løken syndrome, who do not show linkage with NPHP1. Finally, ADPCKD has been shown to be genetically different from NPH1 and genetically heterogeneous [49].

NPH1 has been mainly reported in Europe and North America. In Europe, the "ADMCKD/NPH1 complex," the most frequent genetic cause of chronic renal failure in childhood, accounted for 4.7% of children who started RRT [29]. In the United States, ADMCKD/NPH1 and cystinosis were equally frequent in the pediatric treated ESRD population, representing each 0.7% of incident cases for the years 1992 to 1996 [30]. Cases have been reported in Japan, South America, and Israel, as well as in children of Arab, Turkish, and Indian origin. Within the pediatric ESRD population in the United States, there were, however, no black patients with ADMCKD/NPH1.

### Birth prevalence

Until recently, there were no reliable figures concerning prevalence. The Finnish survey reflects the difficulties in distinguishing between the recessive and the dominant forms [50]. Using familial data on index patients diag-

nosed as having the recessive form of NPH1, Finnish authors estimated that birth prevalence for the years 1963 to 1982 should be 0.13 per 10,000 live births (1 out of 80,000; Table 5). According to the authors, underascertainment is likely since adult patients as well patients not yet having presented typical signs of NPH1 may have been missed. As usual in Finland, a study was undertaken to evaluate whether NPH1 deletion originated from common founders. The founder effect was excluded by haplotype analysis [51].

## BARDET-BIEDL SYNDROME

Bardet-Biedl syndrome (BBS) is an autosomal recessive disorder, genetically heterogeneous, with currently five gene loci. The contribution of each of these loci to the development of the disease appears to depend on ethnic background, BBS1 most commonly occurring in white families [52]. Cardinal manifestations classically include postaxial polydactyly, rod cone dystrophy (leading rapidly to blindness), obesity, male hypogenitalism, and mental retardation. The phenotypic expression of the disease displays not only interfamilial but also intrafamilial variation. As shown by the results of a large survey of patients identified through the Laurence-Moon-Bardet-Biedl Society of Great Britain and through the Guy's hospital Bardet-Biedl Register in the United Kingdom, the clinical variability and the slow development of the clinical features as well as overlapping phenotype observed in Laurence-Moon subjects render difficult the identification of the patients at a young age [53].

Renal abnormalities (persistent fetal lobulation, calyceal clubbing and blunting, cysts or diverticula, scarring, dysplastic kidneys) are particularly common and are even regarded by some as a cardinal feature. Chronic renal failure, sometimes beginning in early childhood, is now reported to be the major cause of early morbidity and mortality. Because of the limited renal investigations usually performed in BBS patients, renal abnormalities and renal impairment are, however, diagnosed in relatively few cases. For example, only 52% of the patients identified in the United Kingdom study had undergone any radiological investigation of the renal tract [52]. Of these, 46% were found to have renal abnormalities. Five percent had chronic renal failure, and 4% were transplanted. In contrast, the prospective cohort study carried out in Newfoundland (Canada) included a complete evaluation of the renal function in all patients [53]. Renal impairment occurred in 25%, with nearly half of them having progressed to ESRD. Ultrasound of the kidneys, performed in 81% of the patients (most having serial studies), disclosed the presence of structural renal abnormalities in 96% of them.

### Pathologic phenotype prevalence and birth prevalence

Two surveys, mostly based on patients ascertained because of visual impairment, allowed an estimation of prevalence (Table 4). In the landmark study by Amman in Switzerland, 57 cases belonging to 26 pedigrees were registered [54]. Most patients were ascertained through a register for tapeto-retinal degeneration. Prevalence was estimated to 0.6 per 100,000. As mentioned by the author, the geographic distribution of the syndrome was not ubiquitous, but was grouped into five distinct regions. Interestingly, 22 of the 57 cases (belonging to 2 pedigrees) were concentrated in central Switzerland, thus suggesting the isolated character of the region. Prevalence reached 5.7 per 100,000 in Newfoundland [55]. In that island, many small communities were founded by a few families originally from the same part of the West country of England or Ireland [56]. Contact between communities was, until recently, by sea and was impossible for several months of the year, and consanguinity was likely to be high in certain parts of the island. However, the scattered distribution of families, as well as the identification of three distinct BBS subtypes, was not consistent with an expectation of a single founder effect. Recently, a founder effect was demonstrated for a group of BBS1 families coming from the same part of the island [56]. In the mixed Arab population of Kuwait, also characterized by a high consanguinity rate, prevalence was found to be 2.8 per 100,000, but a complete registry was not available [57]. Furthermore, two thirds of the patients were Bedouins who constitute an almost isolated population with a multigenerational practice of consanguineous marriages. The prevalence among Bedouins reached 7.4 per 100,000, and birth prevalence was estimated to 1.4 per 10,000 live births [58]. BBS was also reported to be frequent among Palestinian Arab families living in Israel [59].

## NEPHROPATHIC CYSTINOSIS

Nephropathic cystinosis, an autosomal recessive disorder, was first thought to affect only the kidney. With RRT, the disorder appeared multivisceral, with other organ involvement developing with time. These include not only ocular complications (corneal cystine deposition and retinopathy leading to visual impairment), but also thyroid, gonad, and endocrine pancreas deficiency, the possibility of liver and spleen involvement, and finally the risk of muscle and central nervous system complications. The primary defect is a lysosomal cystine transporter deficiency provoking lysosomal cystine storage. It leads to proximal tubular defect, rickets, and growth retardation in the first year of life, followed by glomerular impairment progressing to ESRD at approximately 10 years of age. A French epidemiologic study showed that chronic renal insufficiency occurred at $6.2 \pm 3.5$ years of age and

RRT started at 9.8 ± 2.4 years [60]. It is speculated that early and life-long cysteamine therapy will delay the age of renal failure.

In Europe, cystinosis is the second cause of ESRD in children, after NPH1. It accounted for 3.5% of children who started RRT between 1987 and 1991 [29]. In the United States, ADMCKD/NPH1 and cystinosis were equally common in the pediatric ESRD population. For the years 1992 to 1996, they represented each 0.7% of incident cases of treated ESRD [30]. In French Canada, cystinosis constituted one of the most common causes of ESRD in children. A survey of Canadian pediatric nephrology centers found that 60% of the patients with cystinosis were from Quebec, and of these, the majority were French Canadians [61]. This finding was initially interpreted as consistent with a founder effect caused by the small number of carrier individuals who were present in the founding population of Quebec. Molecular analysis, however, revealed that there are several founding cystinosis mutations with origins both in France and in Ireland, with the Irish mutation having made the most significant contribution to the French Canada population [62]. Conversely, cystinosis is one of the recessive diseases never diagnosed in Finland [43]. Although cystinosis is considered a disorder of fair-skinned individuals of European descent, the disease does occur in blacks, Hispanics, Indians, Pakistanis, and persons of Middle Eastern descent [63]. In the United States, however, 92.3% of ESRD children were white, and there were no black patients [30].

### Birth prevalence

Birth prevalences of 0.06 [60], 0.03 [64], 0.06 [66], 0.09 [67] per 10,000 live births have been estimated in the various surveys conducted in Europe (France, West Germany, and Denmark; Table 5). All authors claimed that ascertainment was nearly complete, but some children may have died without recognition of the underlying diagnosis. Similar values were reported in Australia, where birth prevalence was evaluated through two laboratories performing all enzymatic analyses for lysosomal storage disorders in the country (National Referral Laboratory in Adelaide and Division of Chemical Pathology in Brisbane) [65]. It was 0.04 (1 out of 281,000) for the years 1980 to 1996 in a population predominantly of British extraction. If all births had occurred (that is, in the absence of screening and pregnancy termination), the birth prevalence would have been 0.05 per 10,000 live births (1 out of 192,000). The reasons for the higher prevalence noted in a French region, Brittany, are obscure.

Birth prevalence was higher (1 out of 6237) in the Saguenay-Lac-St-Jean, a geographically isolated region located in Northeastern Quebec [68]. In an ethnically diverse society such as that existing in the West Midlands of the United Kingdom, birth prevalence, evaluated in all neonates by the Neonatal Screening Laboratory in Birmingham for the years 1981 to 1991, was approximately 10 times higher in Pakistanis (1 out of 3613; CI 1 out of 1834 to 1 out of 8378) than among Northwest Europeans (1 out of 46,564; CI 1 out of 27,230 to 1 out of 87,476) [69]. Such a significant difference, not specific to cystinosis, but common to several other inborn errors of metabolism, was interpreted as due to consanguinity in the Pakistani population. Children, however, may have died without recognition of cystinosis. Similarly, most cases reported in Israel were noted in North Africans, a genetically isolated population and in which marriages between relatives were frequent [70].

## PRIMARY HYPEROXALURIA TYPE I

In primary hyperoxaluria type I (PH1), a recessive autosomal disease, the elevated urinary oxalate excretion is due to deficiency of liver-specific peroxisomal alanine:glyoxylate aminotransferase. The excessive production of oxalate leads to recurrent urolithiasis, nephrocalcinosis, progressive renal insufficiency, and then to oxalosis, meaning extrarenal (bone, muscle, artery, eye, skin, nerve, heart, etc.) oxalate accumulation. The clinical spectrum is wide, and patients are seen at all ages. At one extreme, patients present with the most severe acute neonatal form and at the other extreme they may remain asymptomatic until middle age. The survey carried out in Switzerland showed that by the age of 15 years, 20% of patients were in ESRD and 10% had died and that at 25 years, 50% were in ESRD and 20% had died [71]. In Europe, oxalosis accounted for 1.6% of children who started RRT before the age of 15 years between 1987 and 1991 [29]. In ethnic groups with consanguinity such as in Tunisia, PH1 accounted for 18% of children with ESRD, which is 10 times higher than in Europe [72].

The estimation of prevalence in the pediatric population provided by Latta and Brodehl [73] in 1990 was based on German data on ESRD. They noted the following: "*In the registry of the European Dialysis and Transplantation Association about 1% of children developing ESRD every year account for primary hyperoxaluria among those developing ESRD. Our data show 2%–2.7% of children with hyperoxaluria among those developing ESRD. These data are comparable to those of the Arbeitsgemeinschaft für Pädiatrische Nephrologie for 1979–1982. Assuming five to six children developing ESRD per million children and year, the incidence of primary hyperoxaluria can be assumed to be of 1 in 5–15,000,000 children between 0 and 15 years. This figure probably underestimates the true incidence of the disease.*"

### Pathologic phenotype prevalence and birth prevalence

The surveys conducted in Switzerland [71] and France [74] showed the rarity of the disease, although prevalence

in the Swiss survey (0.26 per 100,000) was twice that in the French survey (0.11 per 100,000) in the whole population (Table 4). It reached 0.19 in the 0- to 15-year age group in France. Neither of the studies, however, had consulted urologists, and prevalence may have been underestimated. Birth prevalence, evaluated in neonates through the Neonatal Screening Laboratory at Birmingham, was approximately 10 times more frequent in Pakistanis (1 out of 14,552; CI 1 out of 4001 to 1 out of 119,337) than among Northwest Europeans living in the West Midlands (1 out of 201,777; CI 1 out of 69,023 to 1 out of 977,917) [69]. As for cystinosis, such a difference was interpreted as due to consanguinity in Pakistanis.

## FABRY DISEASE

Fabry disease, a recessive X-linked disorder, results from deficient activity of the lysosomal enzyme α-galactosidase A. The defect leads to progressive accumulation of glycosphingolipids throughout the body. Affected males show angiokeratoma, acroparesthesia, corneal opacity, and hypohydrosis in childhood. With age, they develop disease of the kidneys, heart, and central nervous system. In the kidney, accumulation of glycolipid is noted early in life. Progressive renal failure occurs in the second to fourth decade of life. Generally, female heterozygotes are asymptomatic. Rarely are they severely affected. Most patients are Caucasian, but black, Hispanic, American Indian, Egyptian, and Asian cases have also been observed [75].

The rarity of the disease, its late recognition, and the variability in clinical features expressed in carrier females are obstacles to epidemiologic surveys. As mentioned by Desnick (personal communication), "*The 1 in 40,000 is an estimate based on the frequency of Fabry disease compared with other X-linked disorders. I believe that the disease may be more frequent due to the recent recognition of the milder cardiac variant.*"

### Birth prevalence

As for cystinosis, birth prevalence in the Australian population was evaluated through the results of the two laboratories performing all enzymatic analyses for lysosomal storage diseases. It was estimated to 0.09 per 10,000 live births (1 out of 117,000) for the years 1980 to 1996 [67]. It may be higher since a less severe disease may not have been diagnosed, especially in the adult population. In the Netherlands, the records of the laboratories of the clinical genetic centers involved in the postnatal and prenatal diagnosis led to an evaluation of birth prevalence to be 0.02 per 10,000 live births (or 0.04 for male births) in the years 1970 to 1986 [76].

## TUBEROUS SCLEROSIS

Tuberous sclerosis (TSC) is a dominantly inherited syndrome characterized by the development of hamartomas in many tissues and organs, such as skin, brain, heart, kidney, eyes, and the skeleton. Their number, size, and localization show high variability, and severity can vary greatly within the same family. TSC exhibits locus heterogeneity with two genes, *TSC1* and *TSC2*, the *TSC2* and *PKD1* genes lying adjacent to one another on chromosome 16. Family-based linkage studies have indicated that proportions of TSC due to the *TSC1* and *TSC2* genes were approximately equal [77]. Mainly described in Caucasian populations, TSC has also been reported in black and Asian patients [78].

The kidney is frequently involved, with angiomyolipomas, renal cysts, and more rarely cancers. A survey carried out in Germany and Switzerland showed that 48% of the patients (newborns to 70 years) screened by ultrasonography, computed tomography, or intravenous urography had renal abnormalities (angiomyolipomas in 28%, cysts in 30%, and carcinoma in 0.04%) [79]. No significant phenotypic differences have been discovered between *TSC1* and *TSC2* families, but severe early onset renal cystic disease is associated with deletion involving both *TSC2* and *PKD1* [80]. Renal failure is related to nephronic reduction caused by tumor invasion or to surgery for tumor or hemorrhage. If better management of neurological disorders improves survival, renal involvement might be expected to become a more frequent complication. The prevalence of TSC with ESRD was evaluated at 0.07 per 100,000 in French dialysis centers [81].

### Pathologic phenotype prevalence

Although the highly variable expression of the disease renders the prevalence difficult to establish, TSC was the early subject of a large number of epidemiologic studies [82]. The progressive formulation of criteria has enabled better ascertainment in recent studies [83]. As the disease is the most common dominantly inherited condition causing epilepsy and mental handicap, various authors made estimations of prevalence by studying only TSC in populations of institutionalized patients, thus missing individuals not affected by fits and mental retardation. Because of their small number of patients, the surveys carried out in Scotland [84] and the two successive studies in Olmsted County [85, 86] may not accurately reflect the prevalence. The surveys conducted in the United Kingdom provided approximately similar prevalence values per 100,000, 2.9 within the Oxford region [87], 3.7 in the West of Scotland [82], and 3.9 in the Wessex region [88, 89] (Table 4). Prevalence reached 6.5 [87] and 8.3 [82] in the school-age group. A Japanese survey estimated prevalence at 3.2 per 100,000, close to the British values [90]. The highest prevalence ever

reported, 14.7 per 100,000 in the 11- to 15-year-old population, was found in the western region of Sweden [91]. The authors were aware, however, that a number of cases with late onset or mild symptoms had been missed and concluded that because a number of patients may escape recognition, TSC might be more common than previously believed. In agreement with this hypothesis are the results of a capture-recapture analysis carried out in the Wessex region suggesting that, despite the efforts of the investigators to locate all cases, more than half remain undetected [10]. Thus, the revised estimate of prevalence, taking account of unascertained cases, increased from 3.9 to 8.8 per 100,000 (95% CI, 6.8 to 12.4).

### Mutation rates

As early as 1935, the high frequency of sporadic TSC cases that could be considered as new mutations was noted [12] with a frequency of 60 and 75% in the two British studies [82, 87], and 32% in the Japanese study [90]. From these data, the authors directly estimated the mutation rate at $2.5 \times 10^{-5}$ in the United Kingdom [82, 87] and $1.6 \times 10^{-5}$ in Japan [90]. Calculation of the mutation rate corresponding to each of the implicated genes might be ideally possible by incorporating DNA results into the definition.

## VON HIPPEL-LINDAU DISEASE

Von Hippel-Lindau (VHL) disease, a dominantly inherited disorder, predisposes to a variety of benign and malignant tumors. The most common are hemangioblastoma of the cerebellum, brain stem and spinal chord, retinal angiomas, renal cysts and renal cell carcinoma, pancreatic cysts, pheochromocytoma and epidymal cystadenomas. Phenotypic variability both between families and within families is evident. Interfamilial differences in predisposition to pheochromocytoma reflect the different forms of mutations in the VHL gene. Cumulative age distribution curves seem to indicate that among patients who survive to 60 to 70 years of age, 90 to 95% develop kidney lesions [92]. Cysts are rarely responsible for deterioration of renal function. When it does occur, renal insufficiency is the result of renal surgery performed for renal cell carcinoma. Improvement in screening and treatment of hemangioblastoma of the cerebellum has now promoted renal carcinoma as the leading cause of death.

### Pathologic phenotype prevalence

Von Hippel-Lindau disease has been regarded as a rare disease. However, individuals presenting with only one symptomatic lesion are not always carefully screened for other manifestations, thus leading to an ignored diagnosis. Following inclusion of symptomatic patients as well as first-degree relatives found to present abnormal findings by systematic screening, prevalence was estimated at 2.57 per 100,000 through a single-hospital based study in Germany (Table 4) [93].

### Morbid genotype prevalence

Two surveys, differing by the sources of ascertainment (multiple specialists vs. genetic register), but using the same mode of calculation, were carried out in the United Kingdom (Table 3). Prevalence of heterozygotes was estimated at 1.19 [94] and 1.89 per 100,000 [95]. From the prevalence data in the 25- to 49-year age group, in which ascertainment of heterozygotes appeared likely to be the most accurate, the authors suggested that birth prevalence should be 0.22 [94] and 0.27 [95] per 10,000 live births.

### Mutation rate

As early as 1970, the mutation rate was estimated to be $1.8 \times 10^{-7}$ [12]. Using their prevalence data, British authors evaluated mutation rate; direct estimations gave $4.4 \times 10^{-6}$ in one [94] and $1.4 \times 10^{-6}$ in the other study [95]. In addition, mutation rate was evaluated by indirect estimation in the first study [94]. Fitness was estimated at 0.83 by comparing the number of children born to patients and their normal sibs. The mutation rate was $2.32 \times 10^{-5}$, within the 95% CI calculated by the direct method.

## CONCLUSION

The distribution of genetic diseases in human populations is a function of the combination of different forces such as mutation rate and selection, migration, founder effect and genetic drift, and mating patterns. Since most epidemiologic surveys are subject to a certain amount of criticism, estimations of prevalence in populations should be considered with caution. They might, however, give an order of magnitude. A part of the variation found between populations may be due to methodological differences in the procedure. Consequently, the mode of calculation of prevalence, the definition of the disease and modes of diagnosis, the inclusion of the cases, the sources of ascertainment, the period of time during which events were counted, and the determination of the size of the population have to be clearly compared. In addition, all causes of underascertainment should be analyzed.

Several aspects can remain problematic. Improvement in medical care and in treatment modalities over time may significantly alter survival and thereby enhance the chance of diagnosis during life. Thus, an increase in prevalence may be due to longer survival of patients with renal failure, better ascertainment of the cases, or a combination of these factors. Another point is that prevalence may vary with age. If two populations have a different age distribution, prevalence can differ even if the

risks of the disease for each age are the same in both populations. The major difficulty remains to estimate accurately the number of individuals having a given disease. The characteristic phenotype may not be expressed in some individuals carrying the mutation. For several diseases (for example, ADPKD, TSC, and BBS), standard criteria have been redefined over time so that earlier published numbers might appear of doubtful value. Moreover, because of the insidious nature of some renal disorders, some persons may not recognize that they are affected and so escape medical attention. In addition, because many disorders do not present until later life, ascertainment is often incomplete, and early estimates may be misleadingly low. Because of both rarity and difficulties in diagnosis, it appears that there is still no or little information concerning some diseases, for example, ARPKD, AS, NPS, NPH1, and Fabry disease. The prevalence estimates that are currently used are derived either from the clinical experience of an expert or from the results of a single survey.

Geographic/ethnic variations in single-gene disease occurrence (for example, cystic fibrosis, sickle cell disease) are well known. Until now, figures on kidney diseases essentially applied to populations of European origin. It was only recently that ADPKD [16] and TSC [90] prevalences were estimated in an Asian population, the Japanese. The only survey carried out in a black population, living in the Seychelles, showed an extremely low ADPKD prevalence [24].

Several autosomal recessive diseases have been reported with a high prevalence in some populations, for example, CNF in Finns [42, 45], BBS in Canadians of Western English origin in Newfoundland [56], and in Bedouins [57]. These populations have been living in relative isolation for a long time because of geographic conditions, religious beliefs, or preference. Determination of mutations and their diffusion will help to explain the mechanisms that led to these high values [96].

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