form is soluble and cytoplasmic in mice[6] and man[11]. 2 loci, Got-1 and Got-2 are postulated to be the structural determinants of the soluble and mitochondrial forms of GOT respectively. The 2 GOT isozymes are found with high activity in most tissues. In red blood cells, however, they are not expressed in mouse[6] and only the soluble form is observed in man[11]. We observed relatively high GOT activity in liver, kidney, brain and heart and lower activity in spleen and lung in adults. In general, the enzyme activity per g of tissue was higher in adults as compared to newborns and prenatals which follows earlier findings[6]. Figure 2 also shows that the relative histochemical staining activity of the 2 isozymes is comparable throughout the developmental stages in +/+ individuals. Also, there are no genotype differences observed in the new-borns and adults. In 2- and 3-week-old mice, however, the isozyme patterns are indeed different in the 3 genotypes. In 2-week-old animals the mitochondrial form is absent in dy^{2J}/dy^{2J} and reduced (about 20% of the soluble form) in $+/dy^{2J}$ genotype. Furthermore, in 3-week-old mice, the relative activity of the mitochondrial form is about 30% and nearly equal to the soluble form in dy^{25}/dy^{25} and $+/dy^{2J}$ genotypes respectively.

The genotype differences observed in 2- and 3-week-old animals are of interest because the expression of dystrophy is associated with age. The dy^{2J}/dy^{2J} genotypes show the first sign of dystrophy around day 21. The absence of mitochondrial GOT in dystrophic genotype in 2-week-old mice only suggests that the Got-2 locus itself is not the primary defect of dystrophy. However, the temporal expression of this locus is affected by the dy^{2J} mutation, which could be involved in the expression of dystrophy. The expression of Got-2 locus follows cis rather than trans action of the involved regulatory mechanism. Here the mitochondrial GOT is affected in $+/dy^{2J}$ and dy^{2J}/dy^{2J} genotypes during a critical period of development, just prior to the expression of dystrophy in dy^{2J}/dy^{2J} animals. A number of genetic mechanisms are known to be involved in the processing of structural genes[12]. One such mechanism involves temporal genes, that regulate the developmental programing and are responsible for the appearance and relative tissue distribution of an enzyme during development. These regulatory mechanisms themselves may depend on internal and/or external 'cue(s)' and are not expected to function in isolation. The observed GOT developmental pattern in dystrophy in this report suggests an association between genotype at the dy^{2J} locus and the temporal regulator for the Got-2 locus. The dy^{2J} mutation may provide internal 'cue(s)' for the regulation of GOT and other enzymes that have been implicated to be involved in muscular dystrophy.

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Mendelian recessive ratios in acute poststreptococcal glomerulonephritis[1]

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Summary. A prospective study of 15 families (61 siblings) of index cases of acute poststreptococcal glomerulonephritis detected a proportion of 0.260 ± 0.016 SEM. This is an excellent fit for a single autosomal recessive trait.

Acute poststreptococcal glomerulonephritis (APSGN) is an immune complex disease that develops after streptococcal infection[2]. It appears sporadically in most communities, but in some geographical areas it has an endemic incidence with epidemic outbreaks[3-5]. Familial aggregation of cases has been reported[6], but since there are no recognized markers for a disease that is transient in nature, the difficulty of determining genetic patterns derives from at least 2 considerations; first, the occurrence of asymptomatic cases which are missed in any survey that does not contemplate serial testing of the individuals during the period in which they are at risk, and second that, although some bacterial types have been associated with nephritis, the nephritogenicity (potential to cause nephritis) of a given streptococcus can only be established unquestionably a posteriori, because there is disagreement as to the nature of the relevant bacterial component[7-9]. We have recently reported a prospective family study[10] that took into account the considerations noted above and the present work concerns findings that suggest that susceptibility to develop nephritis may be a mendelian recessive trait.

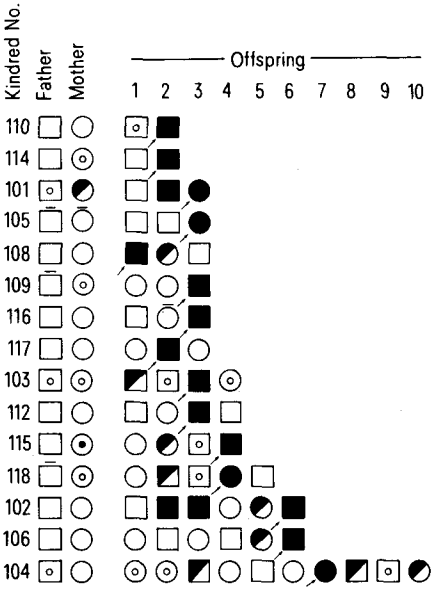
Patients and methods. In Maracaibo, APSGN presents endemo-epidemic characteristics[11]. Since 1977 we have studied in a prospective manner 25 families of patients with clinical APSGN after the appearance of the 1st case (index case) in each family. The study protocol included serial weekly testing of all family members for a period of 4–6 weeks after the detection of the index case (period of close observation) and at least every 6 months afterwards (period of delayed observation). The only condition for selection of these families was the willingness to participate and compliance with the conditions of the study. Details of this work have appeared in a previous communication[10].

On the assumption that only those individuals with a recent infection would be at risk of developing APSGN,

15 families (61 siblings, age range 4–20 years) were selected for analysis on the basis that the siblings had serological evidence of recent streptococcal infection after the detection of the index case in the close observation period. Blood group and histocompatibility antigens (20 antigens in the A series, 32 antigens in the B series, 8 antigens in the C series and 10 antigens in the D series) demonstrated compatibility with the stated first-degree relationship. There was no consanguinity among any of the parents. The HLA testing was performed as described previously[12]. Recent streptococcal infection (defined by the elevation of more than 2 dilutions in antistreptococcal antibody titers with respect to each individual's own values in the period of delayed observation and also with respect to the normal population) was observed in all but one of the siblings reported here. Therefore, 98% of the children were at risk of developing glomerulonephritis since they had an infection with a streptococcus that proved nephritogenic for at least 1 member of the family. Inasmuch as nephritis develops about the time when streptococcal immunoreactivity appears, it is reasonable to assume that the period at risk coincides with the period of close observation.

Group A streptococcus was isolated from 15 members of 13 families. Typing of these streptococci was kindly performed by the Alaska Division of the Center for Disease Control of the Department of Health, Education and Welfare (Anchorage, Alaska) and by Elizabeth Potter's Streptococcal Laboratory at Northwestern University (Chicago, Illinois). 9 streptococci were non-typable for M type, 5 were M type 2 and 1 was M type 63. T types encountered were 8/25/Imp 19, 19 and 4. The site of isolation was the throat in 13 instances and the skin in 2. Clinical evidence of upper respiratory infection was found in only 5 individuals with positive cultures and suspected in 2, who despite streptococcal antibody rise, had negative cultures.

Poststreptococcal glomerulonephritis was diagnosed by the finding of hematuria and/or proteinuria in association with depressed C3 levels (< 100 mg/dl). Clinical disease existed when edema or gross hematuria were noted by the parents or the patient. The absence of symptoms, in an individual with urinary and complement findings, defined subclinical disease. Renal biopsy was done in 13 patients with clinical nephritis but not in the subclinical cases since other authors[13] have shown that the immunohistologic changes of glomerulonephritis are demonstrable in asymptomatic patients with abnormal urine sediment and depressed serum complement.



Acute poststreptococcal glomerulonephritis (APSGN) in families. ● Clinical APSGN, female; ◩ subclinical APSGN, male; ⊙ decrease in C3 without urinary abnormalities, female; ⊡ transient microscopic hematuria or proteinuria without complement changes, male; — lack of evidence of recent streptococcal infection.

Results and discussion. The results are shown in the figure. Clinical APSGN developed in 18 patients (including probands) and subclinical disease was detected in 9 siblings. As reported by others[14], more cases of clinical APSGN occurred in males; however, there is not a statistically significant preferential sex distribution, particularly when all cases of nephritis (clinical and subclinical) are taken into account ($p > 0.2$).

The segregation of parental HLA-haplotypes in affected siblings showed random segregation of paternal and maternal haplotypes ($0.5 < p < 0.6$) in affected siblings of multiple (more than 1) case families.

Correction for single incomplete selection[15] in the sibships gave a proportion of 0.260 ± 0.016 SEM. This is an excellent fit for the expectation in single autosomal recessive inheritance. Correction for multiple incomplete ascertainment does not really apply since the families had only 1 proband (index case); however, the 2 clinical cases in family 101 (fig.) appeared with a difference of only 2 days. If one chooses to consider both these patients as probands, the proband method of Bailey[16] and Morton[17] gives a value of 0.27, again an excellent fit for the theoretical proportion of a mendelian recessive trait. The lack of predominance of either sex is expected in autosomal recessive inheritance.

Previous studies[6,10] have indicated the possibility of familial susceptibility to APSGN. The work of Dodge et al.[6] reported that 19 children out of 91 contacts of index cases developed APSGN. This study involved a single examination of the contacts and did not document recent streptococcal infection; therefore, we feel that the ratio of 0.20 which may be calculated from their data, could represent an underestimation of the incidence of APSGN in the sibships. In our own general study of the attack rate of APSGN in families[10], the calculated ratio is 0.18, which is close to their study, but some of our patients did not have evidence of recent infection and, consequently, were not at risk of developing poststreptococcal nephritis. Because of this fact, we selected the families that are the subject of the present communication.

It is unlikely that with the diagnostic criteria used and the follow-up of the patients, the results could represent an overestimation. It remains a possibility that some cases could have been missed if they occurred outside the period of close observation, but the selection of families without a previous case of APSGN and the long observation period tend to minimize the chances of underestimation of the disease frequency.

It is well recognized that the immune response of the host is the central pathogenetic event in the development of nephritis after streptococcal infection[2] and there is substantial experimental evidence indicating that the antibody response to streptococcal antigens is under genetic control through the expression of a complex trait[18]. The finding of mendelian ratios in acute poststreptococcal nephritis suggest a plausible explanation for the endemic incidence of the disease in certain communities, and not in others with similar socioeconomic and environmental conditions. Solid genetic proof can only be obtained by observing 100% affected offspring of the mating of 2 affected individuals[19].

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Morphometric divergence of Robertsonian populations/species of *Mus:* A multivariate analysis of size and shape

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Summary. The morphological divergence of Robertsonian populations from the Rhaetian Alps (2n=26, 2n=24 and 2n=22) was investigated by multivariate analysis of shape components of the mandible and scapula. These shape components were obtained by a specifically designed multivariate procedure that detects and negates variation in general size. Whilst allozymes frequencies fail to effectively distinguish between Robertsonian populations the above multivariate morphometric procedures showed that the Robertsonian populations are clearly morphometrically distinct and that this morphometric divergence is cladistically congruent with the chromosomal evolution. Given appropriate comparative material, the karyotype of a mouse from these populations can be predicted from the shape of its mandible.

After the discovery that the Tobacco mouse[1] of Val Poschiavo had a 2n=26 karyotype[2] due to Robertsonian fusions of the ancestral (2n=40), acrocentrics many other Robertsonian populations of *Mus musculus* have been found. One of the best known of these is the system of 7 Robertsonian populations in the Rhaetian Alps investigated by Capanna[3] and his co-workers.

The chromosome arms can be identified by their T-G banding pattern and shared (uniquely derived) fusions can be recognized. This has allowed the phylogenetic relationships of these populations to be reconstructed and the process of stasipatric speciation to be investigated[3,4]. Robertsonian fusions tend to lead to reciprocal reproductive isolation between populations due to either hybrid sterility (as a result of failure of meiosis at the 1st spermatocyte), or to greatly reduced fertility in the heterozygote[3]. This process of speciation is thought to be quite rapid (5000 years) on the basis of archeological evidence[3] and the lack of isozyme divergence[5].

Whilst the existence of at least some of these chromosomally distinct populations of *Mus* has been known for some time a recent review of mouse morphometrics[6] revealed no serious attempt to investigate the morphological affinities of these Robertsonian populations.

This paper attempts to answer the following questions. Are the sympatric and parapatric Robertsonian populations morphologically distinct? If they are morphologically divergent, are the cladistic relationships congruent with those hypothesized on the basis of their chromosomal affinities?

4 populations (fig. 1) has been used in this study (represented by 60 specimens). The 3 Robertsonian populations from the Rhaetian Alps are as follows:

1. 2n=26, Upper Valtellina, 2. 2n=24, Upper Valtellina[7], 3. 2n=22, Orobian. The 2n=26 population, which is sympatric with the 2n=24 population, is the well known Tobacco mouse as it is chromosomally identical with the Val Poschiavo 2n=26 population. A population from Burano, South of Orbetello, Tuscany, (2n=40) was used for outgroup comparison.

The phylogenetic relationships of these populations, based on the shared, derived chromosomal fusions, is represented in figure 2.

Some Robertsonian populations (i.e. 24 and 26) do not differ by obvious external features readily recognizable to the human eye. Moreover, they have not yet been successfully distinguished by isozymes frequencies[5]. This is not particularly suprising as both approaches are inferior to multivariate morphometric analysis when it comes to distinguishing between closely related populations of mice[6,8,9]. The morphological character systems chosen for this study were the mandible and scapula since their features can be recorded quickly and accurately. A modified recording procedure[8] allowed us to record 13 mandible and 9 scapula characters by placing these bones on a photographic negative of mm graph paper (reduced 9 times) and viewing them down a binocular microscope (fig. 3).

Since mice grow throughout life it is not possible to distinguish between the influence of ontogenic growth and