One of the unsolved riddles of leprosy, a disease of many riddles, is why some people get it and others do not. Leprosy workers with life-long exposures to the disease rarely succumb, while others with relatively minor exposure may become ill. Children of leprosy patients appear particularly susceptible and many develop the disease even if removed from the household. Rarely, however, do all the children of leprosy parents suffer the same fate.

Striking differences in racial susceptibility have been recorded (8). Europeans are said to be less susceptible than Asians or Africans. This is due, according to some students of the problem, to the development of resistance in Europeans as a consequence of widespread exposure in the

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Middle Ages. This implies that there is an inherited resistance to the disease which developed as the result of exposure over many generations and has been retained to contemporary Europeans. Inherited resistance is less common in populations with only a few generations of extensive exposure to leprosy. There have been some analyses of the inheritance of leprosy as a simple dominant autosomal trait (7, 11), which are suggestive, but by no means prove this mode of inheritance. It is surprising that more family analyses have not been made, since many family data are probably available as a byproduct of population surveys and control programs. It would be useful to publish such data, giving age, sex, family relationship, and type of leprosy in each family member. It is important to include all families ascertained, even those with only a single leprosy member.

There is also a difference in the form of the disease that exposed individuals may develop. Some will have the tuberculoid form, which is usually mild, with a high frequency of spontaneous recovery, and a rapid response to therapy. Others acquire the lepromatous form, which is usually more severe and responds less well to treatment. Lepromatous leprosy is apparently more common in males, whereas tuberculoid leprosy has an equal sex distribution. The ratio of lepromatous to tuberculoid cases varies in different parts of the world.

Lepromatous leprosy is characterized by a peculiar "energetic" state reflected in the pathogenesis of the disease and in the resulting tissue changes. As is well known, lepromatous and tuberculoid cases differ markedly in their reactions to lepromin. Many apparently normal people in both endemic and nonendemic areas develop a characteristic skin lesion when injected subcutaneously with lepromin (positive Mitsuda reaction). Patients with tuberculoid leprosy have a positive reaction, whereas those with lepromatous leprosy never do, even during remissions or after recovery from the disease. Some lepromin-negative healthy individuals may become positive after repeated testing, or after immunization with BCG, which appears to have cross specificity with lepromin. However, there remains a "hard core" of nonreactors who will not convert under any circumstances, and it is from these that the lepromatous cases are presumably recruited.

Dharmendra and Chatterjee (13) have shown that persistently negative reactors are far more likely to develop lepromatous leprosy than individuals who are reactors, or who convert from nonreactors. Beigelman (14), in papers recently published in The Journal, has assembled family data on the distribution of lepromin reactions to test a genetic hypothesis. Although the results are not entirely consistent, the author contends that the capacity for lepromin positivity is inherited as a simple dominant trait, and that this is related to the ability of macrophages to lyse Hansen's bacillus. On this basis one could expect all children of matings in which both parents have lepromatous leprosy to be nonreactors. This was not found to be so, and the writer has provided several cogent reasons to explain this apparent discrepancy.

Even in hyperendemic areas, the nonreactor group is far more common than lepromatous leprosy. Newell, in a very useful review (15), noted that the frequency of lepromatous leprosy never exceeds 1 per cent, even though nonreactors may be 25 per cent or more of the younger population. It has been postulated, therefore, that within the nonreactor group there is a smaller group who lack the "natural" capacity to react to M. leprae; i.e., they lack the "N" factor of Röthberg (16).

In this editorial we would like to develop a hypothesis related to what might be called the "S" or susceptibility factors, which are the reciprocal of the "N" factor. In doing so, we will draw on the subject matter and principles of human population genetics and conclude with a brief presentation of data on a recently discovered system which, on the basis of a limited study in a single leprosy area, appears to have properties expected of an "S" factor. It is recognized that the data supporting this hypothesis are weak, but it is hoped that this presentation may have value in stimulating further investigations.
The following are some of the characteristics expected of "S" factors:  
1. It is probable that there is more than one factor that increases susceptibility to invasion by M. leprae. This could include the ability of macrophages to lyse the bacteria, as suggested by Beiguelman, as well as other factors affecting the reticuloendothelial system, white blood cells, and the immunologic defense system.  
2. One or more of these factors would render the individual more likely to develop lepromatous leprosy than individuals with alternate factors. This effect need not be simply additive; i.e., one factor might have a major effect on susceptibility while others would make only a minor contribution.  
3. Some of the "S" factors could be inherited. If the "N" factor is inherited as a dominant trait, as suggested by Beiguelman's data, then the "S" factor (or factors) could be inherited as recessive traits.  
4. Individuals who had the "S" factors would not necessarily develop lepromatous leprosy. If, however, they were exposed to M. leprae under the appropriate circumstances, those with the "S" factors would be more likely to develop lepromatous leprosy than those with the alternate genotypes, depending on the "N" factor.  
5. The "S" factors would be relatively common in areas of the world where lepromatous leprosy is now common, and less common where the disease no longer exists, or is very rare. As noted in paragraph 3, the frequency of the disease would be less than the frequency of the genes determining "S" factors, since the gene frequency sets the maximum limit of susceptible individuals not all of whom would have the appropriate exposure. Under some circumstances even individuals without "S" factors would develop the disease; however, they should be fewer than those with the factors.  
6. The effect of the "S" factor need not be important throughout life, but might, for example, operate only in youth; natural resistance could be more important in older people.  
7. The genes determining the "S" factors could affect other diseases both in areas of high and of low leprosy endemicity. Since we have postulated that the gene acts on the immunologic system, it would not be surprising to see an effect on susceptibility to other diseases.  
9. The factor would be of higher frequency among males than among females, since, as noted above, lepromatous leprosy is more common in males.  

We have recently discovered a serum protein isoantigen trait that has many of the characteristics of an "S" factor (14). It should be emphasized that the entire argument that this system is related to leprosy is based on a correlation between the trait and lepromatous leprosy in a single study in one geographic area and that our findings have not been retested by ourselves or others. Such studies are in progress. It is presented here as an example of a method that can be used in searching for "S" factors.

For several years we have been studying the development of antibodies against serum proteins in the blood of patients who receive many transfusions (19). In 1964 we found an antibody in a transfused hemophila patient that reacted with a protein present in the serum of an Australian aborigine but was absent in the serum of most normal Americans (10). We could not identify this protein with any of the known serum proteins, and therefore gave it the geographic term "Australian antigen" (Au (1)) (15). Preliminary chemical and immunologic studies suggested that Au(1) contained a small amount of lipid, had the electrophoretic mobility of an alpha globulin, a specific gravity less than 1.20, and a relatively large molecule (2). Using the antisera from the hemophila patient we tested sera from several populations and found Au(1) to be rare in the United States (0.15%) but relatively common in Asian and Pacific populations (Viet Nam 65, Marshall Islands 75, Australian aborigines 56) and less common in Mediterranean populations (Greece 26, Israel 15%).
Ford, Lechat, Cohen, Guinto and others
under the auspices of the Leonard Wood Memorial. Approximately 6 per cent of these
specimens were found to have Au(1). We
were anxious to study the inheritance of
this trait. This was, however, very difficult
to do in the United States, where the trait
is very rare. Through the generous co-
operation of the Memorial and our col-
leagues we went to Cebu to collect blood
specimens from families. The resulting
data, combined with family material col-
lected elsewhere, provided support, though
not proof, that Au(1) was inherited as a
simple autosomal recessive trait (12). Fur-
thermore we found that there was a sig-
nificant difference in the frequency of Au
(1) in the lepromatous as compared to the
tuberculoid cases and the controls. This is
shown in a table taken from the paper
(11) describing this study (Table 1). There is
a higher frequency of Au(1) among males
than among females. There is also an in-
teresting age dependence of the trait. In
the lepromatous cases the frequency de-
creases with age, whereas in the controls
the frequency increases until the 20-39 age
group after which it decreases as in the
lepromatous cases. In the total sample,
there is a linear decrease with age.

The age dependence may have an inter-
esting significance. It could be due to the
decline in amount of Au(1) in an indi-
vidual with the passage of time. Alterna-
tively, the decrease in older age groups
could be due to differential mortality in
respect of Au(1); i.e., subjects with Au(1)
die earlier than those without it and, con-
sequently, their numbers are smaller in the
older age groups. The meager data cur-
rently available favor the latter view.

We have also found that in the United
States, Au(1) is associated with leukemia,
mongolism, Down’s syndrome and other
diseases involving the reticuloendothelial
system and/or white blood cells, but is un-
associated with a variety of other illneces
(8.0). The hypothesis and conjectures that
have been presented are derived from theories
of human population genetics (14). They
bear some analogy to the findings on the

| Table 1. Australian antigen in leprosy patients and nonleprosy controls
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<tr>
<td><strong>Age in years</strong></td>
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<td><strong>Lepromatous cases</strong></td>
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relation of the hemoglobin sickling trait to sickle cell anemia and malaria. Sickle cell homozygotes develop a severe and often fatal anemia. Young heterozygotes apparently are less likely to develop falciparum malaria than individuals with normal hemoglobin; i.e., they are at a selective advantage compared to the normal homozygotes (1,2). There is at present no indication of what protective selective forces might be associated with the Au(1) heterozygote.

From all this one can conclude that Au(1) may qualify as one of the inherited "S" factors. It would be far more convincing, of course, if this association could be found in other leprosy populations, and such studies are in progress. It is probable that there are other traits that qualify as "S" factors, and investigations of various kinds, genetic, epidemiologic, clinical and biochemical may lead to their detection. This, hopefully, would permit the identification of susceptible individuals and the development of prophylactic techniques to protect them.

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