Volume 33, [illegible]
Printed in [illegible]

Leprosy Research Through Genetics

Baruch S. Blumberg, M.D.[1]

I would first like to say how pleased I am to have been invited to speak at this conference and to hear so much about research problems in a disease to which I have had only a superficial exposure. I take it, from what has already been said, that it is best to have had just a superficial exposure to this disease. I am also somewhat overwhelmed to have been asked to speak on this topic when we have in the audience scientists who have concerned themselves with this problem for many years and made contributions to the question of the role of genetics and leprosy. The last clinical experience I had with this disease was some years ago when I was in Surinam and Dr. Bueno de Mesquita very graciously spent a good deal of time showing me the leprosarium at Groot Chatillon. It is good to see him again after this lapse of fifteen years.

In this brief talk, I would like to review the evidence that has been advanced to support the hypothesis that there are inherited factors in leprosy. A selected group of references is appended to this report. The recent review by Spickett ([24,25]) has included much of the available data and I shall rely heavily on that paper in this discussion.[2]

In considering the inheritance of leprosy or other chronic illnesses, there are several hypotheses that can be tested. One is that the disease is inherited in simple Mendelian fashion, i.e., as an autosomal or sex-linked dominant or recessive; or a variation of this. One can also test the hypothesis that inheritance is controlled by more than one gene, i.e., polygenic or quantitative inheritance. There may also be an inherited susceptibility to the disease; i.e., the inheritance of one or more genes renders an individual more susceptible to the illness when he is exposed to an appropriate external agent. Exposed individuals with alternate genotypes would be less likely to become ill, or in some cases would be completely resistant to the illness.

At the outset, one can say that the judgment to be drawn from published reports is the one permitted under Scottish law; that is, "not proven." There is no firm evidence at present in favor of a genetic hypothesis, but there are several intriguing observations that make it clear that the problem should be very actively pursued.

Table 1, taken from Spickett's review, shows the incidence of leprosy in different races residing in Surinam, South America, and shows a considerable difference in the frequency of the disease in these groups. However, it would be very difficult to be certain that in each of these populations the possibilities of detecting illness were the same, and some of the differences may in part reflect cultural and environmental, rather than genetic differences in the populations. Similar differences have been found for Australian aborigine and Hawaiian populations; these are shown in Tables 2 and 3.

There have been some extremely interesting studies on social isolates or semi-isolates (particularly those with high

Table 1.—*Incidence of leprosy in different races from Surinam.*[a]

Race	Population	Number with leprosy
Creole	89,280	874
Hindu	72,960	254
Indonesian	41,280	135
Bushman	23,040	16
American Indian	3,840	4
Chinese	3,120	6
European	3,120	4
Others	3,360	0
Total	240,000	1293

[a]Spickett 1962 ([24]).

[1]Associate Director for Clinical Research, The Institute for Cancer Research, 7701 Burholme Avenue, Fox-Chase, Philadelphia, Penna.

[2]Tables 1, 2, 3, 4 reprinted with permission of *Leprosy Review*.

TABLE 2.—*Incidence of leprosy in Australian aborigines and in those of mixed aborigine-european parentage.*[a]

Race	No. examined	No. with leprosy
Aborigine	4,181	264
Aborigine-European	800	30

[a]Spickett 1962 ([24]).

TABLE 3.—*Incidence of leprosy of different races in Hawaii.*[a]

Race	Incidence
Hawaiian	0.850/1,000
Part Hawaiian	0.480/1,000
Japanese	0.019/1,000
Chinese	0.030/1,000

[a]Spickett 1962 ([24]).

degrees of inbreeding) which have high frequencies of leprosy. One such example is the well-known Venezuelan community of Colonia Tovar, whose population, primarily of German descent, have a much higher frequency of leprosy than individuals of other origins in the surrounding area ([14]). The leprosy clusters of the Acadian populations of New Brunswick and Louisiana have also been studied. When the Norman French settlers of Nova Scotia were expelled in 1775, some went to nearby New Brunswick and others to Louisiana. There is no evidence that leprosy existed in the Acadians prior to their expulsion. However, cases were reported in both of these groups after their removal to their new homes, and they now represent high incidence populations for leprosy in the two areas. There is evidence that the disease may have been introduced independently into these communities. The interesting fact is that both of these genetically related populations appear to be highly susceptible to this disease.

This kind of anecdotal information cannot, of course, prove genetic determination of the disease, but it does provide intriguing ideas for further investigation.

I would now like briefly to review methods used to determine if a disease clusters in families. The method usually followed in the study of a relatively common disease is first to ascertain the cases in the study population. A control group is then selected from the same population which differs from the disease group only in the absence of disease; i.e., they are matched for sex, age, social status, and other factors. The families of both the disease group and the central group are then studied with equal enthusiasm to determine the frequency of the disease. If there is a significant surplus of affected individuals in the families of the disease group as compared to the control family group, then it can be concluded that the disease is familial. It does not follow from this that the disease is inherited. Many purely infectious diseases, for example, tend to cluster in families. The second step in the study would be to determine if the distribution of the disease in the families follows Mendelian segregation; i.e., if its appearance in the generations can be predicted by Mendel's Law. These technics are discussed in textbooks of genetics. It is usually the experience in studies on chronic diseases that the data rarely fit the predictions exactly. Next the concept of penetrance is invoked. This implies that the gene is present in the individual, but its presence cannot be detected. If one has to use very low figures for penetrance, then the interpretation of the data becomes difficult, since in some cases it could also be explained by some nongenetic mechanism. It may also be possible to explain the data on the basis of a more complicated pattern of inheritance. An extension of this is the concept of polygenic inheritance, i.e., that the disease is determined by the combined action of a large and unspecified number of genes.

We can now examine some of the data that have been collected to analyze familial segregation of leprosy. Duarte and Lima examined 9,239 contacts of persons with leprosy and found that nearly 500 had contracted the disease. The relationships of the diseased contacts to the index cases are given in Table 4. However, the method in which the data are presented does not permit an estimation of the number in each category who were at risk, and, although consistent with a family clustering, does not prove it. It has been found that not all members of an exposed sibship develop leprosy; this is consistent with Mendelian

TABLE 4.—*Relationships of affected contacts with the index case.*[a]

Relationship of the index case to the affected contact	No. affected	% of total affected contacts attributable to each relationship
Father	112	24.6
Brother	83	18.2
Mother	76	15.7
Sister	70	15.4
Husband	30	6.6
Wife	24	5.4
Daughter	16	3.6
Son	10	2.2
Uncle	7	1.6
Grandfather	6	1.3
Sister-in-law	3	0.6
♀ Cousin	3	0.6
Grandmother	2	0.4
Father-in-law	2	0.4
Aunt	2	0.4
Friend	2	0.4

Mother-in-law; Nephew; Niece; Brother-in-law; Employer; Acquaintance ♂ Cousin and Daughter-in-law all have 1 affected; that is 0.2% of the total.

[a]Spickett 1962 ([24]).

inheritance but, of course, is consistent with other explanations also.

Spickett utilized two pedigrees of a very large kinship from New Brunswick, published by Aycock and McKinley ([6]) in 1938. He assumed that the ascertainment was complete and analyzed the data using a sibship method, making certain assumptions concerning the genotypes of the parents of the affected individuals. From the data he concluded that the disease may be inherited as a simple autosomal dominant with up to 83 per cent penetrance.

These results are very interesting and indicate the methods that could be used in the analysis of other material from areas of high frequency of the disease where good ascertainment and family studies are possible.

In using the term "inherited susceptibility" one implies that some individuals in a population possess one or more genes which make them more likely to acquire an illness than those with an alternate genotype. The possession of the genotype in itself is not sufficient to cause the illness, but an exogenous agent, such as an infectious agent or an ingested food, must also be present to cause disease. An excellent example of this in the inherited glucose-6-phosphate dehydrogenase trait. Individuals who carry this sex-linked enzyme deficiency are, under ordinary circumstances, normal. However, if they ingest or are otherwise exposed to *Vicia faba* (fava beans) they may develop a hemolytic anemia that can be fatal. A similar reaction occurs if they ingest a variety of drugs including certain antimalarials. This trait is very rare in most northern European populations, but in those populations where it does occur (i.e., the Mediterranean area, Africa) it can be quite common (i.e., 10-40 per cent of males). On theoretic grounds, one would expect some compensatory advantage to the trait to balance the loss of genes from hemolytic anemia and other detrimental effects; there is evidence that the genes confer advantage in respect of resistance to malaria.

Traits of this kind are referred to as polymorphisms. Many of them are known to exist, but in most cases the selective forces operating on these traits are unknown. A list of biochemical polymorphisms is shown in Table 5. (See Blumberg, 1964 ([11])).[3] If there are some genes that confer susceptibility or resistance to leprosy, then conceivably it would be possible to discover which genes they are. However, it is possible to study only those genes that can be identified by use of available methods, and there is no guarantee that these will be related to leprosy. In order to determine if an association exists, a group of patients with leprosy and an appropriate group of controls are studied in respect of each of the traits. If the frequency of a trait is significantly different in the two groups, then an association may exist. A considerable number of studies of this kind have been made primarily with the ABO blood group system and with the inherited ability to taste phenylthiocarbamide. Some of these are referred to in the references to this paper. Dr. Lechat has reviewed the evidence pertaining to the ABO studies and

[3]Table 5 reprinted with permission of *Annual Review of Medicine.*

TABLE 5.—*Biochemical polymorphic traits in man.*[a]

Red blood cell antigens		Serum constituents	
1. ABO		1. Haptoglobin	(Hp)
2. MNS		2. Transferrin	(Tf)
3. P		3. Gamma globulin	(Gm)
4. Rhesus	(Rh)	4. Gamma globulin	(Inv)
5. Lutheran	(Lu)	5. Beta lipoprotein	(Ag, Lp)
6. Kell	(K)	6. Group specific substance	(Gc)
7. Lewis	(Le)	7. Cholinesterase	(NN, DN, FN, etc.)
8. Duffy	(Fy)	8. Phosphatase	
9. Kidd	(Jk)	9. Alpha$_1$ acid glycoprotein	
10. Diego	(Di)		
11. Sutter	(Js)		
12. Sex-linked	(Xg)		

Other cell types		Miscellaneous
1. Hemoglobin	(A, S, C, etc.)	1. Urinary excretion of BAIB
2. G6PD		2. Taste of PTC (T)
3. Red cell phosphatase	(P^a, P^b, P^c)	3. Secretion of blood group substance (Se)
4. Phosphogluconate dehydrogenase		4. Character of ear cerumen (W)
5. White blood cell antigens		5. Inactivation of INH
6. Platelet antigens		

[a]Blumberg 1965 ([10]).

provided important original information of his own. He will, I believe, discuss this later; but, the general conclusion appears to be that no strong association has been detected. The study currently being undertaken on Cebu Island will test the susceptibility hypothesis in respect of a large number of polymorphic traits; publication of these results should contribute to our understanding of this problem.

This concept of inherited susceptibility to leprosy, if correct, may explain in part the striking racial differences in susceptibility to leprosy. European populations apparently had a considerable exposure to leprosy in the thirteenth century. During this period genes that conferred resistance to leprosy would have been at a selective advantage and their numbers would have increased in the population. Hence, over the generations, inherited resistance to the disease in Europe would have increased and the contemporary populations would be relatively resistant to leprosy. Populations that have not had such an exposure, such as some of those from Asia, would not have increased frequencies of the resistance genes and the relative susceptibility would be high. Presumably, this resistance would also increase if the same selective forces operate in future generations.

REFERENCES

1. AUSTIN, C. J. Regional and racial differences in leprosy. Leprosy Rev. **19** (1948) 20-22.
2. AYCOCK, W. L. Familial susceptibility to leprosy. American J. Med. Sci. **201** (1941) 450-466.
3. AYCOCK, W. L. Familial susceptibility as a factor in the propagation of leprosy in North America. Internat. J. Leprosy **8** (1940) 137-150.
4. AYCOCK, W. L. Proposed study of conjugal leprosy with reference to contagion and hereditary susceptibility. Internat. J. Leprosy **16** (1948) 1-8.
5. AYCOCK, W. L. and HAWKINS, J. W. Regional, racial and familial relationships in leprosy in the United States. Pub. Hlth. Rep. **56** (1941) 1324-1336.
6. AYCOCK, W. L. and MCKINLEY, E. B. The roles of familial susceptibility in the epidemiology of leprosy. Internat. J. Leprosy **6** (1938) 169-184.

7. Bancroft, H., Guinto, R. S., Rodriguez, J. and Marques, A. P. A note on familial relationship and the risk of developing leprosy. Internat. J. Leprosy **12** (1944) 79-82.
8. Beiguelman, B. Taste sensitivity to phenylthiourea among patients affected with both tuberculosis and leprosy. Acta. Genet. Med. (Roma) **13** (1964) 190-192.
9. Beiguelman, B., et al. Taste sensitivity to phenylthiourea and drugs with antileprotic effect. Acta. Genet. Med. (Roma) **13** (1964) 200-202.
10. Blumberg, B. S. Differences in the frequency of disease in different populations. Ann. Rev. Med. **16** (1965) 387-404.
11. Blumberg, B. S. Genetic variation of human serum proteins. *In* Sunderman, F. W. and Sunderman, F. W. Jr., Eds. Serum proteins and disproteinemias, Philadelphia, Lippincott, 1964, pp. 27-35.
12. Brown, J. A. Kinnear. The epidemiology of leprosy. East African Med. J. **34** (1957) 351-360.
13. Brown, J. A. Kinnear. Susceptibility and resistance in leprosy. Leprosy Rev. **27** (1956) 147-151.
14. Convit, J. An investigation of leprosy in the German ethnic group of Colonia Tovar in Venezuela. IV. Clinical findings and variations in the Mantoux and Mitsuda reactions observed during five years after BCG vaccination of Mitsuda-negative contacts. Internat. J. Leprosy **24** (1956) 38-44.
15. Degotte, J. Epidemiological leprosy survey in the Nepoko, Kibali-Iture district, Belgian Congo. Internat. J. Leprosy **8** (1940) 421-444.
16. Germond, R. C. A leprosy survey of the eastern border districts of Basutoland, showing the results of strict segregation combined with inspectorate control, and the history of a leper family. Internat. J. Leprosy **6** (1938) 303-314.
17. Hasegawa, K. Über die Blutgruppen bei Leprakranken in Japan. II. Mitteilung. La Lepro **9** (1938) Suppl. 1-2. (Abstract.)
18. Hopkins, Ralph. Heredity in leprosy. Tuberculosis and leprosy; the mycobacterial diseases. Symposium series, V. 1, Lancaster, Penna., American Assoc. Adv. Sci., 1938, pp. 112-118.
19. Hsuen, J., Thomas, E., and Jesudian, G. A.B.O. blood groups and leprosy. Leprosy Rev. **34** (1963) 143-147.
20. Keil, Ernst. Hereditary factors in leprosy. Leprosy Rev. **10** (1939) 163-171.
21. Milesworth, E. H. Evolution of racial resistance to leprosy and other diseases (with special reference to "Leprosy" in "A system of Bacteriology" and to "Lepra" in the "Handbuch der Pathogenen Mikroorganismen.") Acta. Dermat. Venereol. **13** (1932) 201-223.
22. Mukerjee, N. and Ghosh, S. Familial leprosy. J. Indian Med. Assoc. **31** (1958) 129-131.
23. Ryrie, G. A. Regional differences in leprosy; leprosy among Chinese in Malaya. Leprosy Rev. **19** (1948) 4-11.
24. Spickett, S. G. Genetics and the epidemiology of leprosy. I. The incidence of leprosy. Leprosy Rev. **33** (1962) 79-93.
25. Spickett, S. G. Genetics and the epidemiology of leprosy. II. The form of leprosy. Leprosy Rev. **33** (1962) 173-181.
26. Tolentino, J. G. The role of heredity in the transmission of leprosy. Month. Bull. Bur. Hlth. (Manila) **18** (1938) 261-272.

Dr. Sartwell. Thank you, Dr. Blumberg. The next presentation is by Dr. Michel Lechat. Dr. Lechat has been my associate for the last couple of years in a genetic study of leprosy, which he has been conducting in collaboration with our group in Cebu. His talk, however, will be on more general issues. Dr. Lechat is now with the Pan American Health Organization as epidemiologist in charge of Zone II.