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Heredity of Fibrosis of the Pancreas

Possible Mutation Rate of the Gene

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INTRODUCTION

REFINEMENTS in diagnosis have made it possible to distinguish the clinical syndrome of fibrosis of the pancreas from other superficially similar diseases. For excellent descriptions of the clinical appearance, diagnosis and pathology of the syndrome the reader is referred to the papers of Andersen (1947) and May and Lowe (1949).

From a genetic point of view this disease appears to be completely lethal since none of the patients has survived long enough to reproduce. Autopsy of the pancreas in adults has never provided unequivocal evidence of the disease. The failure in the past of the patient to survive and transmit his heredity for fibrosis of the pancreas resulted in the loss of genes responsible for the disease each generation. The rather high frequency of the disease in the population indicates that somehow these losses are recouped and presumably the normal and abnormal genes concerned with the disease are approximately in equilibrium.

What has prevented the extinction of the heredity for fibrosis of the pancreas when each patient perishes without progeny? It is proper to assume that some of the genes lost each generation are replaced by the mutation of normal genes in persons without the disease to abnormal genes which express themselves in later generations. It can be accepted without argument that some of the genes which are lost are replaced by the mutation of normal to abnormal genes. Unfortunately, it is not possible to determine whether the replacement of abnormal genes is due largely to mutation or whether there are other important mechanisms which assist in maintaining the genetic equilibrium.

The purpose of this paper is to report the data we have obtained and to weigh the relative importance of the mechanisms which might be responsible for the replacement of the genes lost with the expired patients each generation. It should be kept clearly in mind that while we present a possible mutation rate for the gene causing fibrosis of the pancreas, we have no way of estimating the probability that mutation is, or is not, the most important factor concerned.

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Our study is an invitation to other workers to contribute data and interpretations to an understanding of mutation rates in man.

Type of Heredity. The earliest suggestion of a definite type of hereditary mechanism was that of Howard (1944) who thought that the disease was produced by a "heterozygous" factor transmitted from one side of the family only. Apparently he thought the disease to be a dominant, the presence of one dose of the deleterious gene being sufficient to produce the condition. If the gene is fully penetrant, the hypothesis of dominance could not be correct, as the gene would become extinct in the generation following mutation and it would be impossible to explain the large numbers of affected relatives observed.

Andersen and Hodges (1946) used genetic techniques to demonstrate clearly that fibrosis of the pancreas appears when a single, simple Mendelian recessive gene is present in the double or homozygous condition. Lowe, May, and Reed (1949) confirmed this conclusion with a different and larger sample of data. In a personal communication, Dr. Cedric Carter, of the London Hospital for Sick Children, states that he has studied the family histories of over 150 cases and his analysis of them gives the same result.

Frequency in Different Racial Groups. Zuelzer and Newton (1949) found that only 3 out of 35 cases of fibrosis of the pancreas were Negroes, and these were probably not "pure" Africans. Thus, only 10% of his cases were colored, though Negroes constitute 35% of the total admissions to the Children's Hospital of Michigan in Detroit.

Personal communications from J. R. Derrick, M.D., at the Charity Hospital at New Orleans and P. D. Trivette, M.D., at the Tulane School of Medicine, New Orleans, revealed no certain case of fibrosis of the pancreas in Negroes, though many were listed for whites. Many definite cases in Negroes should have come to their attention had they existed.

It seems clear that Negroes are afflicted with this disease less often than persons of European descent.

The above is of interest because of the high frequency of sickle cell anemia in Negroes and of thalassemia in Mediterranean countries. Erythroblastosis shows a high frequency among those of European origin and is low among Asiatics. All four of the above diseases demand a high mutation rate, if replacement of the lost gene is primarily by new mutations. All four diseases show sharply different frequencies in different racial groups, with high frequencies in some.

Consanguinity of the Parents. Fibrosis of the pancreas is not a rare disease among families of European origin. Consequently *no* increase of consanguinity among the parents would be expected, nor was any found. Only two cases of consanguineous marriages among the parents of fibrocystic patients have been reported. One instance was observed by Garrod and Hurtley (1913) and the other by Lowe, May, and Reed (1949). The latter found only one first

cousin marriage among the parents of the 118 families studied. This is in agreement with a rate of first cousin marriages of something less than 1% for the U. S. A.

Frequency of the Disease at Autopsy. Andersen and Hodges (1947) report that about 3% of post-mortem examinations at Babies Hospital in New York and at several other hospitals are classified as fibrosis of the pancreas. Harper (1949) reported 3.04% for 755 autopsies at the Royal Alexandria Hospital in Sydney, Australia.

We have obtained, from 19 hospitals throughout the United States, data which indicate that it is correct to utilize 3% as the proportion of hospital deaths coming to autopsy which can be charged to fibrosis of the pancreas.

It should be emphasized that the frequency of a disease at autopsy is *not* equivalent to the frequency of that disease in the general population.

An interesting example of the error which would result from the use of autopsy data as the basis for calculations of the frequency of the disease in the general population may be obtained from the data of Keller and Nute (1949). They reported that of 82,886 admissions of children under 14 years of age to the St. Louis Children's Hospital, 4,669 deaths occurred of which 2,441 were autopsied. Of these post-mortems, 31 cases or 1.27% were diagnosed as juvenile cirrhosis of the liver. Vital statistics of the United States for 1940 record 158,915 deaths of children 14 years of age and younger. Of these, we should expect 1.27%, or 2,018 cases, to have been attributed to juvenile cirrhosis of the liver. However, only 108 deaths were so designated in the same U. S. tables. Thus, 95% of the cases expected to be reported as cirrhosis, on the basis of hospital autopsies, did not materialize. It might be argued that physicians misdiagnose the disease in the majority of cases but this is not a very plausible supposition. It is more reasonable to assume that hospital autopsies represent a biased sample of infant deaths in the whole population. Obviously many accidental deaths of children due to falls, burns, drownings and the like would not have an opportunity to appear in hospital autopsy reports.

Our conclusion is that 3% of cases at autopsy are deaths due to fibrosis of the pancreas, but for a number of reasons, such as the one given above, we cannot use this figure in calculating the frequency of deaths among all infants due to this disease. The result obtained would be too high.

Previous Estimates of the Frequency of the Disease. Andersen and Hodges (1947) used their figure of 3% of autopsy deaths to get a death rate due to fibrosis of the pancreas. In New York State there were 10,804 deaths of children under 14 in 1939. Three per cent of 10,804 is 324 deaths attributed to fibrosis of the pancreas. Dividing 324 by the 187,575 live births in New York State for 1939 gives their published estimate of 1.73 cases of fibrosis per 1000 live births. This value is too high to the extent that autopsy data are unrepresentative of deaths in the whole population. We are indebted to Dorothy Andersen, M.D.,

for sending the above figures to us. We can be certain that the true frequency of the disease is something less than 1.7 cases per 1000 live births, as this figure is definitely the absolute maximum estimate and seems to be higher than actuality.

Lowe, May, and Reed (1949) estimated the range of the frequency for a group of cases at Boston Children's Hospital to be between 1 case per 100 and 1 case per 10,000 live births. Obviously this range is too great to be useful for any precise calculations. Consequently, the range must be narrowed down somewhat before the possible mutation rate of the normal to abnormal gene can be estimated.

The major work of the present paper is the attempt to arrive at a better estimate of the frequency of fibrosis of the pancreas in the general population.

NEW DETERMINATIONS OF THE FREQUENCY OF THE DISEASE

Three sources of information were tapped in order to arrive at a more refined estimate of the frequency of fibrosis of the pancreas. The study was limited to cases receiving attention during the 5-year period from 1945 to 1949 inclusive.

1. Data from "Hospital" Pediatricians. A survey of pediatricians registered as active members of the Society for Pediatric Research or the American Pediatric Society was undertaken to furnish data on the hospital frequency of the disease. In order that no case be reported twice, questionnaires were sent to only one physician at a given office or hospital address. These "hospital" pediatricians were sent an explanatory letter, a reprint of the paper by Lowe, May, and Reed on fibrocystic disease, and a return postcard with the four questions to be answered. These questions follow:

a. Approximately how many hospital admissions of infants and children have come under your care since January 1, 1945?
b. Of these patients, how many had fibrosis of the pancreas?
c. Of all the patients you observed, about how many died? Of these, how many were autopsied?
d. Of those autopsied, about what percentage had fibrosis of the pancreas?

The response to the request for data was satisfactory, 31 out of 60 returned the question card. Since Lowe, May, and Reed (1949) had already presented adequate data for one hospital a comparison of it with that for the whole group should indicate whether the survey technique was valid or not. Table 1 shows that agreement between the two bodies of data is excellent. Consequently we can consider the survey data to be reliable, as a comparison of the two sets of data in a fourfold table gave a X^2 of only 1.08 with a P value between 0.2 and 0.3.

The rate of 1.8 cases of fibrosis of the pancreas per 1000 hospital admissions must be significantly higher than the frequency of the disease in the general

population. This must be so, as a large proportion of children reach the age of 14 years without ever having had a hospital admission.

2. Data from Private Pediatricians. A random sample of approximately 10% of pediatricians in the United States registered with the American Board of Pediatrics was selected. This group was sent an explanatory letter and a return postcard with four requests for data. Since it was anticipated that a 100% response would not be provided, all Minnesota pediatricians registered with the American Board of Pediatrics were surveyed for control purposes. The Minnesota pediatricians who failed to return the data card could be contacted personally and some response obtained from each, thus obtaining a complete sample to compare with the 10% sample for the United States as a whole.

The questions asked of the private practice pediatricians were as follows:

a. Approximately how many newborn infants have come under your care since January 1, 1945?
b. Of these, how many have developed fibrosis of the pancreas?
c. How many of the infants with fibrosis of the pancreas died?

TABLE 1. COMPARISON OF THE DATA FROM LOWE, MAY, AND REED WITH THIS HOSPITAL SURVEY

	LOWE, MAY, AND REED	"HOSPITAL PEDIATRICIANS"	TOTALS
Total Admissions	65,960	237,297	303,257
Cases of Fibrosis of the Pancreas	134	416	550
Rate per 1000 Admissions	2.03	1.75	1.81

d. How many of the patients with fibrosis of the pancreas had siblings or relatives with the disease?

It is gratifying that 46% of all the private pediatricians invited to contribute data, did so. The pediatrician has a busy life and we hesitated to bother him with even four short questions.

It was thought that possibly the practicing pediatricians who responded did so because of having treated a case of the disease, although the introductory letter contained a specific request that they respond whether they had treated a case or not. Half of those responding reported having had *no* cases of fibrosis. It was possible to contact 15 of the 19 Minnesota pediatricians who did not respond to the questionnaire, as a follow-up procedure. Of these 15, we found that 8 had treated at least one case of the disease and 7 had not. There seemed to be no difference between the now "complete" Minnesota group and the small sample (176 responding pediatricians) from the whole registered group in the United States.

The data from the partial sample of United States pediatricians and for the reasonably complete Minnesota sample are given in table 2. The rate is just about one case per 1000 new born infants. This rate is still probably a little

above the actual rate as it probably includes some referrals from non-registered pediatricians, though the explanatory letter asked that referrals *not* be included. Furthermore, many healthy children never see a pediatrician.

There were 241 cases of fibrosis of the pancreas and for 58 of them a relative also was reported to have had the disease. Only 12 physicians volunteered the degree of relationship, 10 reporting a sib with the disease, one a maternal cousin and one a pair of twins both of whom had the disease.

We may conclude that the maximum possible frequency of fibrosis of the pancreas is one case per thousand births, though this rate is probably still higher than actuality.

3. Data from Death Records: We are indebted to Mr. J. W. Brower, Director of the Division of Vital Statistics of the Minnesota Department of Public Health for permission to search the records, and to Miss Gladys Casady and staff for aid in searching.

Death records for the years 1945–1949 are codified according to the 5th Revision of the International Listings of Causes of Death. Because that edition

TABLE 2. DATA FROM PRIVATE PRACTICE PEDIATRICIANS

	UNITED STATES PARTIAL SAMPLE	MINNESOTA "COMPLETE" SAMPLE	TOTALS
Total Newborn Reported Seen	207,323	19,653	226,976
Total Cases of Fibrosis	222	19	241
Rate per 1000	1.1	1.0	1.06
Deaths	94	8	102
Mortality Rate	42%	42%	42%
Number of Affected Relatives	53	5	58

did not list fibrocystic disease as a cause of death, it was necessary to examine *all* the records in code groups in which fibrosis might logically have been placed. Since the oldest case reported in the United States died at 17 years of age (Gibbs, Bostick, and Smith, 1950), the search was limited to deaths of persons 20 years of age or less.

The code groups considered to contain all deaths due to fibrosis of the pancreas were:

107—Bronchopneumonia, including capillary bronchitis.

119—Diarrhea, enteritis and ulceration of the intestine.

122b—Intestinal obstructions.

128—Diseases of the pancreas excluding diabetes mellitus.

157g—Congenital malformations of the digestive tract.

158—Congenital debility.

161a—Asphyxia. Occasionally what is primarily bronchopneumonia is reported as asphyxiation.

From the 1,687 death records pulled according to the classifications above,

there were 23 found to include fibrosis of the pancreas as some part of the medical certification. In addition, 3 records which were selected as probable cases were found to be diagnosed cases of fibrocystic disease when followed up (2 at the University of Minnesota and one at the Mayo Clinic), though the death records themselves did not mention the disease. We consider these 26 deaths to be positive cases of fibrosis of the pancreas. Only 2 of the children were over 5 years of age at death, one 6 and the other 7. These last two were not born in the 1945–1949 period so must be omitted in the following calculations of rate at birth, leaving 24 cases, all of them having been born during the 1945–1949 period.

The total births in Minnesota during 1945–1949 inclusive were 343,604. Of these, 24 were known to have died of the disease. However, these 24 are only a fraction of the total number of cases of fibrosis in the population of births during 1945–1949; the remainder had survived beyond January 1, 1950. Table 2 shows that of the cases known to pediatricians, 42% had died by 1950. Consequently, the 24 reported deaths are only 42% of the total number of cases in the 1945–1949 population of births, and the total number expected including living and dead is 57 children.

We are reasonably certain that of the 343,604 births an absolute minimum of 57 had developed fibrosis of the pancreas during the first five years of life. All 108 cases for which Lowe, May, and Reed had information had shown first symptoms of the disease before they were 16 months old. Consequently, we assume that almost all children with the genotype for the disease, born between 1945–1949, had shown symptoms during that five-year period.

The absolute minimum rate of fibrosis of the pancreas is therefore 343,604 divided by 57, or 0.16 cases per 1,000 births. It would be foolish to consider this low value to be the true rate for the disease. Many cases must have been born and died in rural areas without coming to the attention of a physician familiar with the diagnostic signs. Undoubtedly many cases were certified simply as bronchopneumonia or intestinal obstruction.

Returning to the 1,687 death records pulled to include all possible cases of fibrosis, there were 74 selected as probable cases of the disease. These were selected according to extremely conservative criteria and are only those records where information was unusually detailed. None of these mentioned fibrosis of the pancreas as such but in every case the evidence seemed adequate for a probable diagnosis of fibrosis of the pancreas. There were many sorts of evidence used. For instance, one of the deaths considered "probable" was the younger brother of a girl reported to us by the University Pediatrics Department as a positive case. Yet the boy himself never got to a registered pediatrician.

If we accept the selected 74 "probables" as genuine, we must adjust by the 42% mortality rate which gives a total of 177 "probable" cases. We may then add the 57 positive cases to the 177 probables and get 234 cases. These divided

by 343,604 give a rate of 0.68 per 1000 live births. Even with this addition we must have missed some cases. It would seem reasonable to accept the figure, however, as the minimum possible frequency of the disease, with the expectation that it is lower than the actual rate.

4. Summary of the Frequency Data. The purpose of this experimental work was to narrow the range of frequencies between one case per 100 and one case per 10,000 live births as reported by Lowe, May, and Reed (1949). This was done and the range can now be considered to be from 0.68 cases to one case per 1000 live births. It is assumed that the true rate is somewhere between these rather narrow limits, and probably closer to the upper one of one case per 1000. Rounded off, the range is from 0.7–1.0 per 1000 live births.

CALCULATION OF THE POSSIBLE MUTATION RATE

If the calculation of the mutation rate for any recessive lethal character is ever defensible, it would seem proper to do so for fibrosis of the pancreas. If acceptable, the calculation of the mutation rate is simplicity itself for a recessive lethal. Briefly stated, if the alleles concerned are frequent in the population, and at equilibrium, while the survival and reproductive fitness of the heterozygote is the same as that of the homozygous normal, we find that the mutation rate per chromosome per generation is equivalent to the frequency of lethal children in the population.

Consequently the possible mutation rate for the normal to abnormal gene for fibrosis of the pancreas is between 0.7×10^{-3} and 1.0×10^{-3}. This is a very high mutation rate compared with those which are well established for the lower organisms. Obviously it is suspect because it is at one extreme of the range of mutation which we might expect to find. However, the extreme variants of a series of mutation rates are real and must not be rejected merely because they find themselves among the extreme values. Let us look at the objections to accepting calculations of the mutation rates for recessive lethal characters. These have been clearly stated by Haldane (1948).

The first objection is that the normal and abnormal alleles are not in equilibrium, due to the recent breakdown of isolates. This objection is not so important for a *common* gene such as that for fibrosis of the pancreas, as it would be for a rare gene.

An indication of how frequent the abnormal gene is can be obtained from the estimated frequency of affected individuals. They may be designated as q^2, in the expression $p^2 + 2pq + q^2$, where q is the frequency of the abnormal allele and p the frequency of the normal allele. Using our frequency range for the disease of 0.00068 to 0.001 the values of q are 0.026 to 0.032 and the frequency of the heterozygote, 2pq, is from 0.051 to 0.063. In other words, one person in every 16 to 20 carries the gene for fibrosis of the pancreas, a surprisingly common gene.

A more powerful objection is that the heterozygote might have greater

survival value, reproductive fitness, or both, compared to the normal homozygote. The differential fitness in favor of the heterozygote might account for the maintenance of the defective gene in the population. We have no way of testing what the survival of the heterozygous and homozygous normal genotypes may be. It is possible to speculate as to the productive fitness of the heterozygote as measured by the average number of non-diseased children produced. Using the data of Lowe, May, and Reed (1949), there were 365 children from the heterozygous parents and of them there were 167 with the disease. These 167 were not expected to live long enough to reproduce. This leaves 198 children produced who could be considered as potentially reproductive. These were divided among 110 families for an average of 1.8 children per family who might be expected to reproduce. Obviously, this low average is not enough to maintain the group, though it must be remembered that some of the families were not completed at the time of the study, and that those heterozygotes who produced no abnormal children because of their small family sizes are not available for the study, and cannot be found.

Glass (1950) has suggested that persons having one or more erythroblastotic children compensate for the loss of them by additional pregnancies. It is generally known that in those urban communities where family size is controlled efficiently enough to make compensation necessary, not enough children are produced for replacement. Consequently, groups that intentionally compensate for their losses but at the same time fail to replace themselves could not increase the frequency of the abnormal gene in the population as a whole.

The opinion of C. D. May, M.D., who has worked with fibrosis of the pancreas for many years, is that compensation would not operate extensively and that the prolonged illness and heavy hospital expenses of the sick children would discourage the heterozygous parents from having the normal sized family which they might have planned.

The fact that only a small superiority of the heterozygote in survival, reproductive fitness, or both, would be necessary to replace the lost genes, without resorting to mutation at all, would make studies attempting to measure the difference, if any, between the heterozygote and the normal homozygote unusually difficult. An insoluble problem, at present, is that of detecting those heterozygotes who have not produced an affected child. Without them we cannot estimate the biological effectiveness of the heterozygote compared with the normal homozygote.

In view of the above, experimental attempts to determine the role of mutation in replacing losses of the fibrosis genes would not appear likely to succeed.

DISCUSSION

A marshalling of opinions as to the role of mutation in replacing the loss of genes for fibrosis of the pancreas, via the death of the affected children, will

not prove anything. However, a short discussion might stimulate thinking about mutation rates in man, an important scientific problem.

It was mentioned previously that there are now four human characters known which demand high mutation rates, if mutation is the mechanism by which the gene losses are replaced.

1. Neel (1950) reported that the gene causing sickle cell anemia in Negroes would have to mutate at a rate of 1×10^{-2} chromosomes per generation, a truly staggering figure, as he points out.

2. Next most disturbing, because of its high rate, is the disease, fibrosis of the pancreas, reported here to have a rate of from 0.7 to 1.0×10^{-3}.

3. With erythroblastosis, it is more difficult, though not impossible to allege that the replacement of the lost genes is via the superiority of the heterozygote, because it is the heterozygote that dies of the disease. In this case the prevalent notion is that genetic drift, or some mechanism other than mutation, brought about a high frequency of the rhesus negative genotype in early European tribes, of which the Basques are a present day remnant. We are of the opinion that it would be difficult for genetic drift to bring such a condition about in any appreciable number of people with strong selection, say of 5% deaths among the heterozygotes, against the rhesus negative genotype. Furthermore, the rhesus negative genotype must be fairly high in other regions, such as Africa, because the frequency of the rhesus negative "gene" in American Negroes is about 29.2%. A good proportion of this frequency must have come from Africa as it is not generally considered that American Negroes have more than 50% white genes.

It seems more logical to us that the Basques are the remnants of people showing a high mutation rate to the rhesus negative allele rather than the flotsam of an early European tribe with a rhesus negative gene frequency of over 50%.

What would the mutation rate have to be to replace the rhesus negative genes lost via erythroblastosis?

Haldane (1942) points out that the effect of selection against the rhesus negative "gene" per generation is given by the equation:

$$dp/dt = kp^2(1 - p)(p - \tfrac{1}{2})$$

Where dp/dt is the rate of change in the frequency of the rhesus negative gene, k is the selection against the heterozygote, and p is the frequency of the rhesus negative gene. With p equal to 0.39 for the American white population the expression equals $-0.0102k$. Haldane sets k at 0.05, so that our change in the frequency of the rhesus negative gene each generation would be -0.00051. This is equivalent to the mutation rate per chromosome per generation that would be necessary to replace the losses. The mutation rate would be expressed as 5.1×10^{-4}.

It would seem that the mutation theory of replacement should be given prominent consideration along with the other theories previously elaborated.

4. Neel and Valentine (1947) calculated that if the heterozygote has normal viability, equilibrium would be secured by a mutation rate of 4×10^{-4} from the normal gene to that for thalassemia. They also point out that if the heterozygote had an increased fitness of only 2.1% there would be equilibrium without any mutation at all. Once again we cannot decide between the two major alternatives.

The above four diseases not only agree in that they call for high mutation rates, or superiority of the heterozygote, but also in showing sharp differences in frequency for different racial groups. It would seem that all four are explicable in the same way, whatever the answer may be.

Is it improbable on *a priori* grounds that such high mutation rates exist? Stadler (1948) found a mutation rate in *one* race of *Zea mays* at the R locus of 1.82×10^{-3}. Castle (1951) has collected data from several sources and shown that the average value for mutations at the hooded locus in rats is about 1.4×10^{-4}. It would seem that the human diseases under consideration could well be at this high end of the mutation spectrum.

Reed (1941) showed clearly that Drosophila heterozygous for several different visible "Marker" genes were distinctly inferior in viability, and presumably in reproductive fitness, to the homozygous wild type. Stern and Novitski (1948) showed that a large majority of lethals in the heterozygous condition decrease viability. Even their 2 lethals (out of 33) which seemed to give the heterozygote clearly increased viability were not certain to have had greater reproductive capacity also. There is, indeed, very little precise evidence that the heterozygote for a *particular pair of alleles* is superior to the normal homozygote. It sould seem more reasonable that usually the physiology of the heterozygote is intermediate between the two homozygotes.

The facts are not yet available which would allow a scientific choice between the alternatives of a high mutation rate or the superiority of the heterozygote as the main mechanism of gene replacement involved in the four diseases discussed here. The detection of mutants in the sickle cell anemia project by Neel may answer the question, by inference, for all four diseases. While we are more inclined toward the acceptance of high mutation rates rather than even slight superiority of the heterozygote, there is always room for an entirely distinct and novel explanation of the population genetics of these four most interesting diseases.

SUMMARY

Fibrosis of the pancreas is a simple recessive trait which causes the eventual death of infants and children and genetically speaking, is a lethal. It seems to be fully penetrant.

A comparison and evaluation of data from three sources, hospitals, pediatricians in private practice and death records indicate that the frequency of the disease lies between 0.7 and 1.0 case per 1000 live births. These are the genetic homozygotes all of whom die and with each death the two recessive genes involved are lost from the population. If it is assumed that these lost genes are replaced by mutations from the normal to abnormal allele, the mutation rate per chromosome per generation is equivalent to the frequency of the disease, i.e., 0.7 to 1.0 $\times$ 10^{-3}. This assumes a very high mutation rate, and is suspect because it is so high.

It is pointed out in the discussion that the four highest mutation rates suggested for man, all of which are high enough to invite further study, agree in that they show very high frequencies in other races. It would seem that the answer for all four diseases is the same and the alternative explanations for the replacement of the genes lost via the lethal individuals are either high mutation rates or superiority of the heterozygotes. The present authors are inclined toward the hypothesis of high mutation rates though probably the majority of geneticists would favor superiority of the heterozygote, at least at first glance.

The four diseases are assumed to have mutation rates almost of "ever-sporting" magnitude, and the rates assumed for them, are given below:

Sickle cell anemia	1.0×10^{-2}
Fibrosis of the pancreas	0.7 to 1.0×10^{-3}
Erythroblastosis	5.1×10^{-4}
Thalassemia	4×10^{-4}

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