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Phenylketonuria – a problem in eugenics

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For academic purposes, eugenics is defined as the study of agencies under social control that may improve or impair the racial qualities of future generations either physically or mentally. This formula allows many different interpretations. The subject matter might involve almost any material studied in medicine, psychology or social science. In the light of knowledge of its frequent misuse, inclusion of the term ''racial'' in the definition seems unfortunate. A racial quality is presumably any character which differs in frequency or which (when it is metrical) differs in average value in two or more large groups of people. No qualities have been found to occur in every member of one race and in no member of another. Furthermore, as Morant (1939) has shown in his analysis of European populations, differences between average measurements in the so-called races are often much smaller than commonly supposed. The qualities by which people differ can be treated as legitimate material for scientific investigation without employing any invidious concept of race. The human race constitutes the field of eugenic inquiry.

A popular view of eugenics, which has in the past been encouraged by propaganda groups such as eugenic societies and human betterment foundations, implies active interference in human reproduction. The general grounds for interference are often held to be that civilisation has tended to reverse the process of natural selection because the weaklings are now being fostered at the expense of the naturally strong. Not only are the physically and mentally inferior prevented from perishing in infancy by the activities of medical and social services but also, when the weaklings grow up, they are supposed to be more fertile than the normal. As Karl Pearson (1909) once put it, ''we have suspended the racial purgation maintained in the less developed communities by natural selection.'' Degeneration of the physical and mental level of civilised peoples is believed to be inevitable unless eugenic measures are taken to counteract it.

When Galton first proposed the word ''eugenics'' to describe the science of improving stock, he was evidently influenced by observations on the results of breeding accomplished by animal fanciers with horses and hounds. Applied to man, the object of selective breeding would be, in Galton's (1883) words, ''to give to the more suitable races or strains of blood a better chance of prevailing speedily over the less suitable than they otherwise would have had''. This appears to imply that eugenics should endeavour to accelerate natural selection between races. A narrow conception of eugenics thus emerged at the outset. I think it is perfectly safe to assume that, if Galton had foreseen the extremes to which ideas concerning ''race hygiene'' would be taken in some countries, he would not have placed emphasis on the propaganda aspect of the study. A broader view of the aims of eugenics was, indeed, expressed by Galton in his correspondence with Bateson as recorded by Pearson (1930), where a steady though slow amelioration of the human breed was held to be a reasonable objective.

The best antidote to pernicious ideas based upon emotional bias lies probably in spreading knowledge about established facts, but these facts must first be brought to light. Research in the early days of the Galton Laboratory followed the direct method of measuring and recording human qualities without considering the details of their genetic determination. The biological units of

inheritance, however, are genes or similar entities and not the visible characters. For some qualities the superficial approach involves no loss of accuracy. If the effects of a set of genes are independent of environment and separately recognisable, like the MM, MN, and NN blood types, or even if their effects are perfectly additive, characters can be used as precisely as genes for eugenic purposes. Recessivity, however, interferes with the character in the gene. In the case of a rare recessive character the correspondence between presence of the gene and presence of the character is very weak. The offending genes are maintained in the population almost entirely by the transmission through normal heterozygotes or carriers. These people carry the gene, but its presence is not manifest. Many rare recessive disabilities have been identified in man, and doubtless many more lie awaiting detection. Not improbably, about two people out of every three are carriers of at least one serious recessive defect. These recessive genes pose a problem which should cause the propagandist of popular eugenics to pause and consider. The early eugenists, as I have mentioned already, feared the loss of the beneficial effects of natural selection. If we are to accept Fisher's (1930) theory of the evolution of dominance, the prevalence of these rare recessive abnormalities is partly the result of natural selection. In any event, it is certain that natural selection has failed to eliminate them. They present a real challenge to eugenic science.

clinical picture

The points raised concerning the aims of eugenics and its relation to natural selection are perhaps most easily appreciated by studying a practical example. Phenylketonuria is a rare disease, first observed by a Norwegian biochemist, Fölling (1934). The essential feature is the urinary excretion of about 1 gramme daily of phenyl-pyruvic acid, a ketonic acid with the formula $C_6H_5.CH_2.CO.COOH$. The excretion is usually continuous throughout life and has been observed in infancy. Occasional cases showing intermittent excretion have been recorded. Every case so far examined has shown intellectual defect. This is commonly of a severe degree, amounting to imbecility or idiocy. The name ''phenylketonuria'' (Penrose and Quastel 1937) seems preferable to the original more cumbersome designation ''imbecilitas phenylpyruvica'' or to ''phenylpyruvic oligophrenia,'' favoured by American workers. The shorter designation emphasises the biochemical nature of the abnormality and brings the nomenclature into line with that of other comparable abnormalities, such as alcaptonuria, cystinuria, and pentosuria.

The *test for phenylpyruvic acid in the urine* is so simple and striking that the failure of clinicians to observe the reaction until so recently is puzzling, except on the basis of the difficulty of obtaining specimens from subjects of low mental grade. When the acid is present, a deep bluish-green, which fades within a few minutes, is obtained on the addition of a few drops of 5% ferric chloride solution. If desired, alkaline urines can first be neutralised by the addition of dilute sulphuric acid. The urine also has a detectable aromatic odour. Naturally, Fölling's discovery stimulated other people to look for cases, and success in this respect was reported first in Great Britain, and then in France, the United States, Switzerland and Canada.

The clinical picture is peculiar in many ways. To the casual glance these patients appear to be just ordinary imbeciles, but the skilled observer may occasionally diagnose a case correctly before the urine has been tested. Some 60% of the cases are of the idiot grade and 30% imbecile. Most of them are good-tempered, and those with sense enough to learn to talk are co-operative and friendly. In the low-grade cases digital mannerism, so-called hyperkinetic phenomena, are often conspicuous. Some of the patients, who are severely affected mentally, have epileptiform seizures in infancy, and occasionally the attacks continue up to the age of 9 or 10 years, but I have not known them to occur in older patients. Phenylketonuria has been ascertained more frequently in

females than in males, but this difference may be because females are healthier and live longer than the males (table 1). There are more females among the ascertained cases in this sample, but more males died in infancy who might have been affected.

Among the main distinctive physical features are dwarfing of stature and reduced head measurements as compared with the normal average. The incisor teeth tend to be widely spaced, and the skin, which may show pigmented patches, is unduly subject to dermatitis. There is sometimes a tendency to excessive sweating. Kyphosis is very common. On the neurological side the constant feature is accentuation of all reflexes, both superficial and deep, in a manner reminiscent of the brisk responses obtained in hyperthyroidism. Abnormal quantities of creatine are excreted in the urine (Pugh 1940). Ordinarily there is no paralysis and no increase in muscular tone, though Jervis (1937) asserts that spasticity is a typical finding. Fair hair and blue eyes are very common characteristics. In some patients the hair is colourless as in the albino. Comparison of hair colours of the imbeciles with those of their normal brothers and sisters indicates that the fair hair is part of the abnormality, though, as with normals, the colour may darken with maturity. On the whole, the physical health of these patients is surprisingly good, and I know of only two instances of the patient's death in an institution followed by autopsy. In one of these instances I found multiple nerve tumours (Penrose 1939). In another, kindly reported to me by Dr. R. M. Stewart, similar nerve tumours had not been noticed.

Table 1 – Ages of Phenylketonurics

Age –	Males				Females			
Group	CL	CD	PD	Total	CL	CD	PD	Total
60–69	•	•	•	•	•	1	•	1
50–59	1	•	•	1	2	•	•	2
40–49	2	•	•	2	3	•	•	3
30–39	3	•	•	3	7	•	•	7
20–29	8	•	•	8	13	•	•	13
10–19	20	2	1	23	17	•	3	20
0–9	8	•	17	25	7	1	8	16
Total	42	2	18	62	49	2	11	62

CL, certain cases (living). CD, certain cases (died).
PD, possible cases (died).

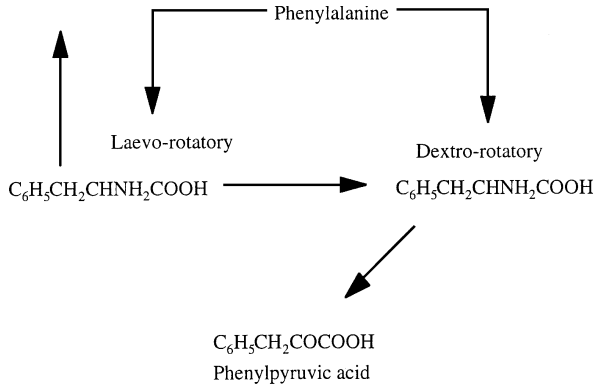
The patient had died of carcinoma of the thyroid gland. There were numerous small pigmented moles on the skin and one large pedunculated lipoma. The question whether there is a real tendency of phenylketonurics to develop nerve tumours needs further investigation, together with the rest of the pathological anatomy. In both these autopsies, however, the ferric chloride test for phenylpyruvic acid was made on all tissues with negative results.

CHEMISTRY

The pathological chemistry of phenylketonuria has received a lot of attention, but there are many problems here still unsolved. The two main questions are (1) where the phenylpyruvic acid comes from, and (2) how the defect, which allows this abnormal metabolite to be excreted, is related to the associated mental and physical peculiarities. The quantity of the acid excreted depends on the diet. It can be increased by feeding either laevo- or dextro-phenylalanine, and temporarily abolished by a protein free diet. After a few days of a protein free diet, however, a

patient starts to again to excrete the acid, which must then be derived from endogenous metabolism. Feeding with excess of amino-acids other than phenylalanine, such as tyrosine and alanine, does not increase the quantity of phenylpyruvic acid in the urine. Thus, it is very probable that phenylalanine, although a common and necessary constituent of ordinary diet, is the source of the abnormal metabolite.

After feeding *normal* subjects on phenylalanine in sufficient quantities, phenylpyruvic acid can be detected in the urine.



A dose of about 15 g of the laevo variety is needed to produce this result, but 0.5 g of dextro-phenylalanine is sufficient. This may indicate that, normally, laevo-phenylalanine is changed to dextro in the body and that the dextro substance is deaminised in the kidneys and liver by the enzyme discovered by Krebs (1935).

Only traces of the acid have been found in the blood of affected imbeciles, but a definitely high concentration of laevophenylalanine is demonstrable. Evidently, in the abnormals, some enzymes capable of splitting the phenylalanine or the phenylpyruvic acid are absent. It is uncertain how far the detrimental effects of this absence are due to poisoning by the excess of phenylalanine and phenylpyruvic acid in the system, or how far they are due to starvation caused by the inability of build up essential metabolites. The disturbance of reflexes resembling thyrotoxicosis suggest active poisoning, but the lack of pigmentation and of normal physical growth suggests nutritional deficiency. By studying the cerebral blood-supply in phenylketonurics, Himwich and Fazekas (1940) found that their low level of mental activity might be attributed to diminished rate of oxidation.

Animal experiments have led to fascinating results – e.g. those obtained by feeding albino rats on laevo-phenylalanine. Feeding these animals with the dextro-substance always leads to phenylketonuria, as it does in man. In acid solution, however, the laevo substance produces nothing abnormal. In neutral solution it leads to phenylketonuria, but in alkaline solution it produces alcaptonuria (Fölling et al. 1938). Thus, three rare conditions known in man, *phenylketonuria*, *alcaptonuria* and *albinism*, have been brought into close chemical relationship with one another. Obviously, this is a field where biochemistry has a great contribution to make towards the understanding of human inheritance. By analogy with work on the genetics of plant pigments, the aid of the biochemist will be needed in sorting out the genotypes and allelomorphic genes.

HEREDITY

Pedigrees of phenylketonuria can be interpreted without much hesitation as demonstrations of the mode of inheritance of a rare recessive mendelian trait. The main features include significant familial incidence, which is practically always confined to brothers and sisters. There is sharp segregation between normal and abnormal members of the family. Cousin parents, also, are frequent.

The recessive hypothesis has been further strengthened by calculating the probable magnitude of the familial ratio of affected to normal members in sibships after making due adjustment for mode of ascertainment. The ratio is very close to 1 in 4. Except in two families in the United States cited by Jervis (1937) where the mother was phenylketonuric, parents have been reported to be of about average mental capacity. In the great majority of instances they have been examined and proved not to be excretors of phenylpyruvic acid. In the 56 families of which I have records the parents were all normal; 39 brothers or sisters of propositi were affected and 153 were normal. Five pairs (9%) of the parents were first cousins. Jervis found 5% of the parents of the patients from the United States institutions to be first cousins, and 14% of the parents from the Norwegian patients were first cousins (Fölling et al. 1945). All these percentages are significantly higher than the frequencies of first-cousin marriages in the general populations concerned, which is probably below 1% and may be as low as 0.6%. The summary in table 2 shows also that, if the initial case discovered in each sibship is set aside, the ratio of affected to normal among brothers and sisters is 129/509 (25.3%), very close to 1 in 4.

Since we are dealing with a defect due to heredity the problem of controlling the incidence apparently ceases to be a medial question and becomes a matter of pure eugenics. This view, however, is incorrect. There may be methods of alleviating the condition, even though it is inborn, in a manner analogous to the way in which a child with club-feet may be helped to walk, or a child with congenital cataract enabled to see. Attempts have been made to produce improvement of phenylketonurics by giving them massive doses of thiamine (Bates 1939) because of the known effects of this vitamin in stimulating the metabolism of pyruvic acid. No success has been reported, although lack of this vitamin makes phenylketonuria easier to produce in experimental animals. This does not mean that the possibilities in the field are exhausted. However, consideration of the associated abnormalities, such as small size of the head, might tend to make us cautious about expecting anything like a cure. Easily measurable environmental agencies, such as those connected with maternal age and order of birth, do not appear to be of significance in determining the incidence of phenylketonuria; but there may be undiscovered influences which help to determine the severity of the defect.

Table 2 – Families of Phenylketonurics

Source	Initial cases	Brothers and Sisters		Parents		
	Phk.	Phk.	Normal	Phk.	Normal	First Cousins
Munro and Penrose (1939)	56	39	153	0	112	10
Jervis (1939)	125	72	270	2	248	14
Fölling et al. (1945)	22	18	86	0	44	6
Total	203	129	509	2	404	30

If phenylketonuria is viewed as a problem of preventative medicine, there are also difficulties. Two genes are required to produce the condition, one derived from each parent, but we cannot take the same attitude here that we might with regard to some noxious pest and simply ask to have the offending genes exterminated. The frequency of the condition in the general population was estimated by Munro (1939) to be about 1 in 50,000 in the United Kingdom and by Jervis (1937) to about 1 in 25,000 in the United States. In Norway the incidence may be a little greater. These incidence frequencies are likely to be approximately correct, because they agree fairly well with the observed proportions of first-cousin parents when the Lenz-Dahlberg formula is applied. The high incidence in Norway may, however, be illusory, because the distribution there was found

to be uneven, and there was a tendency for some of the cases to be concentrated in isolated districts where inbreeding was unavoidable. In one small region, Hvaler, a single ancestor possessing the gene might have been responsible for the four certain and two probable cases found there. Judged by institutional surveys, the incidence is high in France (Rhein and Stoeber 1936) and low in Switzerland (Brugger 1942).

The gene frequency, or square root of the incidence, must vary between 1 in 158 in the U.S.A. and 1 in 223 in the U.K.

Survey	*Case frequency* (q^2)	*Gene frequency* (q)	*Carrier frequency* (2q (1-q))
U.S.A.	1/25,000	1/158	1/80
U.K.	1/50,000	1/223	1/112

The frequency of carriers of the gene is double the gene frequency, because the gene may be on either one of a pair of chromosomes. Hence, the frequency of carriers in this country is of the order of 1 in 100. To eliminate the gene from the racial stock would involve sterilising 1% of the normal population, if carriers could be identified. Only a lunatic would advocate such a procedure to prevent the occurrence of a handful of harmless imbeciles. Sterilisation of the affected imbeciles would do no good, except in the very rare cases where they might be expected to have offspring. The attempt to reduce the frequency of the genes by assuming close relations of affected cases to be carriers and sterilising them necessarily involves many errors. Such a plan would leave far the largest reservoir of genes – that in the general population – untouched.

In spite of the alleged interest taken in the subject of hereditary disease in Germany, no search for phenylketonurics has been reported there. If such a search had been instituted, a curious situation might have arisen; for, up to the present time, no phenylketonuric of Jewish origin has been discovered, though cases of German, Irish, Italian, Slavonic and Dutch origin were found in the U.S.A. Moreover, there were no cases found among American negroes. This picture, as seen in table 3, is a somewhat refreshing change from that presented by Tay-Sachs disease (the infantile form of amaurotic idiocy), whose incidence is almost confined to Jewish communities. A sterilisation programme to control phenylketonuria confined to the so-called Aryans would hardly have appealed to the recently overthrown government of Germany.

Table 3 – Racial Origins of Phenylketonurics

Origin	Observed percentage of 161 cases*	Expected (1920 census)‡	Ratio of observed to expected
Latin	18	4.8	3.8
Slavonic	10	2.8	3.6
Dutch	3	1.1	2.7
Irish	21	10.1	2.1
Scandinavian	2	2.4	0.8
German	6	9.0	0.7
English	12	32.1	0.4
Jewish	0	2.3	0.0
African	0	7.4	0.0
Total	72	72.0	1.0
Other	28	•	•

* Jervis (1939) ‡ adapted from Burr (1922)

The high percentage of Irish and Italian cases in the American sample is of interest. In his survey of cases in the United Kingdom, Munro (1939) found a rather higher incidence in the west of

England than in the east, particularly in the north-west. We had the impression that there were many cases of Celtic origin. The distribution of the blood antigens, A- and B, in phenylketonurics and their sibs showed a higher incidence of B than did the English populaiton from which these cases were drawen, though the incidence of A was not raised. That is to say, these families tended to resemble groups of peripheral Europeans in respect of their blood-group frequencies expressed as percentages:

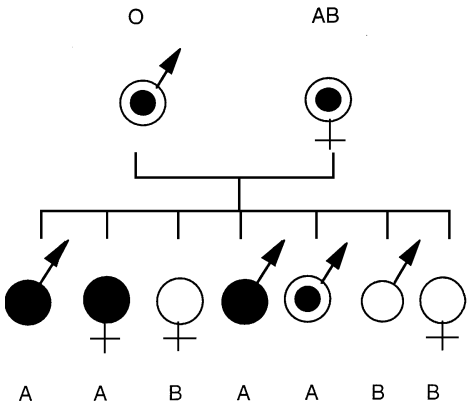
Sample	*O*	*A*	*B*	*AB*
Phenylketonuria sibships (179)	45	39	13	3
England (9000)	47	42	8	3
Northern Ireland (784)	56	30	12	2
Southern Italy (1460)	49	29	19	3

Although we cannot yet say what is the original habitat of this gene, or how often it has arisen by new mutation in more than one place, at least it is proved that it determines a ''racial'' quality in the technical sense that its frequency differs in different parts of the world.

Before taking any steps in practical eugenics, the effect already produced by natural selection on phenylketonuria should be studied. Out of more than 500 reported cases, only three families are known to have had any offspring (Jervis 1939). Affected persons are in general, extremely infertile. On the other hand, the families in which cases occur are no smaller than the average size of the community. While nature takes care to eliminate nearly all the genes which occur in homozygous (duplicate) form, she does not eliminate the gene in heterozygous (single) form, where its action is masked by the presence of other genes. If Fisher's (1930) theory of the evolution of dominance is correct, some of this masking of carriers may be actually the result of a natural selection which has encouraged the spreading of genes which tend to alleviate the condition.

The argument can even be applied to the imbeciles. Not all are equally affected. The degree of mental defect does vary within the families, where more than one case occurs, but there appears also to be some tendency for the grade to be of the same level in the same sibship. On the basis of somewhat limited material I estimate that the correlation of mental grade of affected sibs is of the order of +0.3. This value suggests that differences in mental grade can be due to genetic modifiers. The way in which such modifiers might be supposed to act is shown in a Canadian sibship (Penrose 1945). The parents, of English origin, had 5 living affected children besides 6 normal children. Two of the phenylketonurics were idiots, two were imbeciles, and one was a simpleton or moron with severe juvenile diabetes. The two imbeciles had glycosuria and may have been mild diabetics, but the two idiots never showed glycosuria. Is it possible that the diabetes, which is presumably an incidental condition of genetic origin, in this sibship actually modifies and alleviates the manifestation of the phenylketonuria. The general tendency mentioned earlier for females to be more healthy than males may also be due to selective modification because of the relatively higher fertility of females as compared with males (Penrose 1942).

Reverting to the discussion of the heterozygtes or carriers, we may ask whether there are to be observed in them any traces of the effect of the abnormal gene which have not been blotted out by selective modification. This is to say, perhaps the gene is not perfectly recessive. Observations on families in which phenylketonuria has occurred give, on the whole, very little ground for supposing that carriers are in any way abnormal. However, I have come across several families in the course of my investigations or those of Munro (1939) where depressions associated with persecutory ideas were frequent in close relatives. The mean age of onset of the mental disturbance in 20 members of such families was about 50 years. Fölling, Mohr, and Ruud (1945), in their Norwegian studies, doubt the significance of these findings. The family histories of American cases, however, gave my



A sibship of phenylketonurics, showing blood groups. If linkage is complete normal A sibs must be carriers and B sibs may or may not be carriers. (Circles indicate normals; central dots indicate carriers).

theory some support, though the mental illness found in relatives were all diagnosed as schizophrenia. If there is variation in the degree of manifestation of mental symptoms in the phenylketonuric homozygote, we may expect an even greater degree of variability in any mental symptoms associated with the heterozygous state. However, if the concealment of the gene in heterozygous form is to be attributed to nature we may admit that in her task she has been, on the whole, very successful.

DETECTION OF CARRIERS

Another line of inquiry is the search for a functional test to differentiate carrriers from the normal. At first it seemed as though experiments might demonstrate that the parents of phenylketonurics and other probable carriers had a low threshold of tolerance for doses of phenylalanine or of phenylpyruvic acid as compared with the normal average. Fölling (1934) thought that parents were liable to spontaneous excretion of phenylalanine. It now seems that, if there is any biochemical difference between carriers and the average person, it is very difficult to detect. Perhaps the right test will yet be discovered.

A quite different approach to the problem of detection of carriers is the search for closely linked genes which can serve as markers. Here we are no longer attempting to improve the degree of positive correlation between the character and the gene. The effects of a linked gene can be negatively or positively correlated with those of the abnormal gene. The most straightforward test to make – i.e., that for linkage with genes on the sex chromosome, which can be either partial or complete (Haldane 1936) – gives negative results when applied here. The gene we are concerned with is evidently located upon one of the autosomes. The search for autosomal linkage is an arduous task and requires the co-operation of personnel with a variety of skills. The investigation carried out on the relation of phenylketonuria to the ABO and MN antigens by Munro et al (1939) occupied about two years merely to cover all the known English cases. Some additional information has been obtained from affected Canadian families. No indication of linkage is discernible between phenylketonuria and MN, but with ABO there may be a relatively weak linkage, with a recombination value of 30%. The accompanying figure shows a family of the type which favours the linkage hypothesis. However, even if this linkage is real it is too weak to warrant using the ABO blood groups alone as markers for carriers.

EUGENIC PROGNOSIS

The situation at present is, then, that we are for practical purposes still unable to identify carriers. Persons who are related to phenylketonurics, nevertheless, inquire whether they are likely to have affected children, and they must and can be given information.

Let us take the case of the normal brother or sister of a phenylketonuric imbecile. His chance of being a carrier is 2 in 3. Unless he chooses a wife who is a cousin of his or an inhabitant of the Norwegian Hvaler islands, she will have the ordinary chance being a carrier, and this has been shown to be of the order of 1 in 100. The chance that a child of this union will be affected is, therefore, a quarter of two-thirds of a hundred – i.e. 1 in 600. In my opinion, this risk is no adequate ground for discouraging the union.

There is, however, a wider eugenic aspect. Are we justified in allowing the further spread of a noxious gene in the population! Here I think we must accept the inevitable, which is not, after all, very bad. It is obviously unfair to discriminate between one carrier and another regarding which shall be allowed to have offspring and which not, and we cannot reasonable sterilise 1% of the population. The practical medical aim is to reduce the incidence of phenylketonuria. This can be accomplished by preventing consanguineous matings in affected families, and ultimately by preventing all matings of two carriers. These procedures are, paradoxically, slightly dysgenic. Haldane (1939) has calculated that the general tendency in recent years for the degree of inbreeding to diminish in human populations will actually tend to produce a slight increase in the abundance of carriers in most rare recessive diseases. The point is that in the past there has probably been balance between extinction of genes (through infertility of affected homozygotes) and new mutations. The proposed eugenic practice of discouraging the mating of partners who are both carriers denies, as it were, natural selection its legitimate prey. The argument, however, is contingent on the normal fertility of carriers. Mutation of the gene for phenylketonuria, moreover, is probably not sufficiently frequent to cause any alarming increase in carriers for a long time to come.

ENVOI

I have dwelt at length on the subject of phenylketonuria partly because it is fascinating in itself and partly because it demonstrates many of the problems of eugenics as they appear in the light of recent knowledge. The topic also emphasises the need for close co-operation between the clinician, the biochemist, the serologist and the geneticist. It is impossible for anyone to solve all the problems concerned single-handed. As in other branches of scientific work, groups of experts must be the units of the eugenic investigations.

Another attraction of the study of phenylketonuria is its psychiatric implications. The general problems of mental health is among the most important problems confronting the human race. We do not, in civilised communities, willingly entrust persons judged to be insane or mentally defective with dangerous weapons such as knives and firearms. Now that weapons are constructed capable of instantaneous annihilation of large populations, the question of ensuring the intelligence and mental stability of people entrusted with power of decision has become extremely significant. Failure in the the psychiatric field could make the other most elaborate plans for improving the human race quite valueless. Up to now the contribution of human genetics to the study of psychiatry, except in Huntington's chorea and other uncommon neurological conditions, has been vague and often misleading. In phenylketonuria we have an instance where a detectable chemical deviation is associated with abnormal mental function. The discovery raises two important questions: (1) whether some other types of mental illness will not be found to have hereditary bio-

chemical backgrounds, and (2) how far the course of such illnesses when identified, can be influenced by the deliberate alteration of body metabolism.

Progress in knowledge of the hereditary factors involved in mental diseases has been greatly hampered by lack of accurate methods of discriminating one type of disease from another. Until other conditions can be specified with an accuracy approaching that which has been obtained in phenylketonuria, eugenic prognosis in the field of mental illness will remain, in most instances, a surmise based upon personal bias rather than a scientific judgment.

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