A NOTE ON THE FUTURE OF PHENYLKETONURIA

By

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THE new clan of treated phenylketonurics (1) cannot be assumed to be a happy one, or one with a high proportion of well adjusted individuals. Conceding for the moment that the phenylketonuric, if he sticks to his diet, will retain much of his intelligence, it is safe to predict that he will be miserable. One of his life's basic processes for satisfaction, his food, has been seriously tampered with, and replaced by a conflict. Eggs, milk, cheese, meat, fish, poultry, most fruit, even ordinary bread, are taboo for his table. He will consume a diet which will be cunningly prepared and flavoured, but he can hardly say that he "eats food". His fate is that the satisfaction—and the surcease—of incorporating various articles of food does not exist for him, or only in an attenuated form.

More than this, the legitimate diet permitted him conceals risk. He must plot a careful course between the Scylla of too little phenylalanine and the Charybdis of too much. Too little will lead to tissue breakdown, generalized amino-aciduria, and return of the old biochemical abnormalities (2). Too much will intoxicate his neurones and start his progression down the slippery slope of mental dullness. The margin for error in a given case may not be great.

So the act of eating, instead of being pleasurable, is beset with difficulty and anxiety of a degree which the diabetic, or even the obsessional neurotic, never encounters. Furthermore the phenylketonuric child will learn guilt as the response to natural appetite, while he is too young to appreciate that it is not his craving that is dangerous, so much as the medical progress which has landed him in his predicament.

How will the poor phenylketonuric handle these problems? Because he is not likely to be of exceptional intelligence or adaptability, it is not going to be easy for him to find satisfaction compensating for all this. The less stable ones will not need to turn to alcohol for oblivion to the burden imposed by medical science. All they have to do is substitute milk or some such beverage for the vine with which disappointed Omar Khayyam, in that profane poem, proposed to fill "another and another cup to drown the memory of this impertinence". They can cloud their consciousness on bacon and eggs. So the process of evolution, helped by medicine, presents us with a distinctive neurotic escape manœuvre, which I have termed "Protein Addiction". No doubt we shall figure out a Greek name for it when the time comes.

I am not so artless as to believe that many people are interested in phenylketonuria, but most of us are interested, in theory at least, in preventive psychiatry, or mental hygiene as it is usually called. Those of us who have enough energy left over from our daily psychiatrizing to read articles on mental hygiene, may recognize two groups. The larger group stresses the value of improving child-rearing practices and family life. These are excellent and encouraging articles, even if their recommendations are vague. Presidential Addresses are in this group. The other, smaller group stresses inheritance, and morosely accuses

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medicine of interfering with natural selection, and atomic radiation of interfering with the gonads, spoiling our heredity by stealth. Mention is made in the latter articles of the futility of Freudism (psychoanalysis is always called Freudism, perhaps to rate it with Lamarckism), and of man tinkering with his own destiny by means of absurd eugenic programmes.

So we find this two-fold approach to the problems of mental hygiene. As C. D. Darlington (1954) observes, the notions of heredity and environment have chased one another round the workshops of biology for a hundred years. What I like to point out is the curious divergence in emotional tone which exists between the two groups of articles.

The first group is invariably encouraging. The second is distinctly gloomy. Now it is hard to see how the facts of dynamic psychiatry make for optimism about the subject on which the facts of genetics make for pessimism. The explanation of this divergence may simply be that manic, cheery boys become dynamic psychiatrists and that depressive, fatalistic boys become geneticists and genetic psychiatrists.

The Advantages of Therapy

This new treatment of phenylketonuria, beautifully but painfully, points up the old difficulties. In the literature of the subject we read of the advantages of the new treatment.

Dr. Woolf, Professor Moncrieff and Dr. Griffiths (1955) have summarized them for us. They comment on the low cost of the diet when compared with the benefit it will bestow. They write:

> "The economic aspects of this form of treatment must be considered . . . The special dietary constituents . . . cost 10/9 a day at present prices. If all phenylketonuric aments came under treatment and some form of central manufacture of the special diet ingredients could be organized, the cost would fall considerably. The grades of many of these patients might be raised so that the ineducable became educationally sub-normal and the E.S.N. group might get accepted at ordinary schools. Later on, society may gain productive members."

As a footnote they add that, since their article went to press, the cost has been reduced to 7/4 per day.

An obvious difficulty in this programme—not, I think an insuperable one—is to diagnose enough infant phenylketonurics, that is phenylketonurics young enough to give the diet a reasonable chance. We know that if cretins are neglected in their early months, they have missed their chance of normal physiological and psychological maturation. The trouble with phenylketonuric babies is that, unlike cretins, they look normal and are not diagnosed until they reach an advanced age—such as 2–3 years—when it becomes obvious that they are defective. Very rarely, a phenylketonuric baby has the chance of being diagnosed if he already has a phenylketonuric sibling, and the family doctor is on the look-out for the condition.

Now with all respect to those working on the therapy of phenylketonuria, I want to suggest that it is not ideal to supply this expensive diet to four-year-old children, or even one-year-old children, when with a little additional ingenuity it should be possible to supply it to all phenylketonuric infants shortly after birth. This would involve testing all babies just prior to their departure from the maternity hospitals. A simple test consisting of ferric chloride splashed on a damp diaper, taking a few seconds to perform, and rarely requiring a confirmatory test, would be adequate. A large jar of ferric chloride solution could be kept in the foyer of the maternity hospital. Each infant could be

splashed on the diaper by the bell-hop just prior to the proud father taking delivery of what would then be a guaranteed non-phenylketonuric child.

Of course, the biochemist would first have to calculate that, by the time this graduation ceremony was held, sufficient phenylalanine in the form of milk had been ingested to ensure that the urine test of phenylketonuric babies would be positive. The hospitals supplying this service would for preference be large and situated in the U.S.A. because of the high incidence there. It would take time, but there is little doubt that sooner or later the phenylketonuric babies would be picked up. And in the course of a generation, thousands of phenylketonurics would be spared the usual belated diagnosis, and would have an opportunity of therapy in the vital first year of life. Well, these prospects certainly seem agreeable—but let us look at the disadvantages.

The Disadvantages of Therapy

The main catch in this delightful programme is that although society, in the words of Woolf and Moncrieff, "may gain productive members", their most notable product is going to be a steady supply of more phenylketonuria.

Phenylketonurics at the present time, because of their mental level, rarely have progeny; this causes a loss of phenylketonuric genes in each generation. If we assume that the incidence of the disease is in a state of equilibrium, there must be some counteracting influence keeping up the frequency of the gene in the human genetic pool. Otherwise it would disappear. This influence is two-fold. Mutation is one possibility. Slighter greater fertility of the carriers is the other.

With the advent of therapy, there will be three instead of two influences maintaining the gene in the population: mutation, greater fertility of the carriers, and direct transmission by phenylketonurics themselves. The progeny from the mating of a phenylketonuric and a non-carrier normal will all be carriers, though having normal phenotypes. Half of the progeny of a phenylketonuric and a carrier will be phenylketonuric, the other half carriers.

With this increasing frequency of carriers, the frequency of phenylketonuria now rises from its present low level until a new equilibrium is established, which depends on the success achieved by therapy, but more resembles the order of frequency of, say, red-haired individuals in the community.

In this account of the mounting frequency of phenylketonuria, we have assumed that mating is at random. This is unjustified; human mating does not take place at random. Marriages are between members of a social group, and, up to a point, between people living in the same area.

My opinion is that phenylketonurics will tend to form a relatively compact ingroup with a high proportion of intermarriage. Why? The affliction will draw the subjects together, much as deaf-mutes are drawn together and tend to intermarry. Phenylketonurics will come together in clinics, schools and treatment centres as children whilst they must be conditioned or disciplined to adhere to their diet, and the necessity for consuming the same artificial diet as adults will isolate the ingroup still further from homes in which a normal diet is served. Despite the good intentions of both ingroup and outgroup, meal-time social intercourse between phenylketonurics and normals will be inconvenient and even embarrassing. The phenylketonuric, like the vegetarian, will naturally prefer to consume his diet, other things being equal, in the company of somebody doing likewise. Yet another factor which may narrow the phenylketonuric's choice of a sexual partner to his peers is his decreased

intelligence, if we may assume that intelligence will not be perfectly restored by therapy.

So we will have intermarriage. Here is the rub: intermarriage between phenylketonurics will result in progeny *all* of whom will be phenylketonurics. Assuming general intermarriage, the frequency of phenylketonuria would double itself in the first generation after the initiation of treatment. Furthermore, unions between persons below the line in intelligence are above the line in fecundity, if only for the reason that dullards are not so smart with contraceptive devices. When we compared just now the frequency of the phenylketonuric gene in its new equilibrium to the frequency of the gene for red hair, the estimate was probably too low. For unlike the phenylketonurics, red-heads are presumably average in respect of intelligence and proficiency with contraception. Above all, red-heads do not form an ingroup prone to intermarriage. (I am prepared to grant that sexual selection, as far as I am concerned, operates favourably for the female red-head.) In this way the frequency of the gene for red hair remains at what we assume is an equilibrium. But intermarriage would speed up the rate at which phenylketonuria will reach what would be considered today a fantastically high incidence.

Sharp Controversy

This plunges us into the sharp controversy which sometimes exists between the ideals of preventive medicine and those of therapeutics. It is a controversy of ethics, and the medical practitioner is not obliged to take a consistent stand either for preventive medicine or for therapeutics, whatever the Hippocratic oath may say. Conceivably he can change sides, with different illnesses and different individuals in question. In the case of phenylketonuria he may consider, for example, that the possibilities of treatment are appalling, and that the disability at present produced by the untreated disease in the total population is slight, so that he is justified in withholding therapy, against the interests of the individual, but for the greatest good of the greatest number. There would, of course, be little point in figuring all this and withholding therapy, if the enthusiastic therapist next door were dispensing it.

What we will need here is some concerted policy for our guidance. The difficulty is, where are the wise men who will formulate the policy? Let us call on the geneticist. One expects the specialist in genetics to take a longer view of human suffering than the specialist in medicine, who has to treat the individual, if only to earn his living. The geneticist can afford the luxury of the long view. The following comments were made by a geneticist (3) before the advent of therapy in phenylketonuria gave the problem its newest piquancy. I am quoting them as representative of a line of thought which too occasionally blunders into the holy places of medicine.

"The full dangers of propagation unrestricted by disease were not realizable before the end of the nineteenth century. But Malthus' discussion suggested the idea of natural selection to both Darwin and Wallace. The dangers of genetic decay and the possibilities of genetic improvement had been indicated by Plato . . . To put the matter in another way: the limit to the population of men that the earth will carry is set by the physical character of the earth and the genetic character of men . . . The principle that is being applied to meet this crisis is the principle that the State—and even the World State—should accept responsibility for the nutrition, health and education of all human beings from

the time of conception to the end of life. This principle can be easily and immediately justified by the view that individuals who are not properly cared for in these respects are an incubus, and may be a danger, to society. But it is a principle with a corollary. The State of mankind cannot accept a responsibility which goes back as far as the fertilized egg without one day claiming the right to go further and control the quality or proportions of gametes which go to make the fertilized egg. Fertilization is, as we have tried to show, an important event. But it has antecedents. It is not so important that all responsibility should begin after it, and none be allowed before it.

"How this control can properly be exercised is the deepest problem that confronts humanity today. But, although deep it is not remote. If we fail to think it out quickly enough we shall be faced with the continuance on a grander scale of the old methods of preserving balance. We shall be faced with war, famine, and disease . . ."

What an eloquent warning this is! Even granting my earlier hypothesis about depressive boys becoming geneticists, we cannot discount its force. Inspired, can we claim "the right to go further and control" phenylketonuria? After all, the practical difficulties are not great. It would simply be a matter of deciding which of two devices to use:

(*a*) not to treat it, or
(*b*) to sterilize those treated.

But this sort of procedure is known as negative eugenics, and negative eugenics is repugnant to medicine at the present time. Admittedly it has a bad record, and perhaps the Eugenic Courts of the Third Reich are too fresh in our memories.

Even among the sincere attempts at negative eugenics, few if any have been founded on adequate knowledge. The sterilization of epileptics is the prime example. Forel, in Switzerland, suggested their sterilization on eugenic grounds as long ago as 1892, well before the rediscovery of the science of Mendelian genetics. In 1907 Indiana (U.S.A.) first introduced legislation for sterilization, and at present such laws exist in many states. The first European state to adopt legislation was the Swiss Canton of Vaud, in 1929. Denmark, Germany, Sweden, Norway and Finland followed shortly after (4). When eventually it was decided that idiopathic epilepsy does not possess the precise basis of heredity which had been assumed for it, the medical profession naturally became cautious of making wholesale negative eugenic recommendations.

Nevertheless the medical profession can overdo this caution. It is fair to say that the medical representatives of the eugenics movement have taken up a strong position—on the fence. Confronted by the increasing relaxation of natural selection brought about by medicine, of which phenylketonuria's example is the best (or worst) yet, they have become conscious as never before of the contra-indications to negative eugenics.

These contra-indications were summarized by a second professor of genetics (5) as follows:

(*a*) Our ignorance of human genetics may induce us to make mistakes.
(*b*) The problem of the dividing line; who shall arbitrate regarding sterilization of cases of moderate defect only?
(*c*) The possibility of unscrupulous use of negative eugenics by certain ideologies—as with the Nazi party; "what coalition of minorities will decide what other coalition of minorities is undesirable?"

The professor concluded "Nothing I can think of could do the unfolding study of human heredity, with all its broad implications, more harm than premature

attempts to apply that knowledge in any dogmatic fashion to as complex an issue as man has ever tackled".

Professor, had you phenylketonuria in mind when you wrote that? Your three deterrents do not deter us for long here. They could be answered in some such way as this:

(*a*) The mode of inheritance of this condition is unusually well established. It would be unduly modest to say we were ignorant of it.

(*b*) The dividing line does not exist between this condition and the normal. Either the condition exists or it does not. And, happily, a chemical test and not one of us psychiatrists, decides.

(*c*) It is difficult to conceive of a political body with ulterior motives with respect to phenylpyruvic acid in the urine. The zeal and aggression which has characterized the eugenic movements of the past, is not likely to be invoked here.

If I may borrow as analogy from the author just quoted, the position of the physicians who treat phenylketonuria will be similar to that of the settlers who, in good faith but ignorant of the ecological disaster they are risking, introduce a pest such as the rabbit to a new country. Once the pest is established the strictest vermin laws may be ineffectual. Analogously, the simplest time to control the incidence of phenylketonuria—assuming we want to control it—is right now, before the problem reaches the proportions to which successful Bickel-Woolf type therapy will inflate it.

Envoi

This is a new issue of an old coin.

I asked two colleagues to criticize it, which they did with genial vigour. Their objections and scepticism ought to be mentioned here, being important because of their frequent occurrence amongst medical men.

Colleague No. 1 said that it was not his place to doubt that the new therapy would do what its inventors claimed. What he doubted was that the medical profession would ever be silly enough to treat phenylketonuric infants in any numbers. He held the opinion that my warning was overdrawn, because, he said, "these things have a tendency to control themselves". Euthanasia was unofficially practised, he said, despite the official dictum about it, and so, he said, doctors would "unofficially" tend to ignore infants with phenylketonuria and to provide no treatment.

That is what he said. I have only been able to think of three things that might explain it. Was he one of those cheery, manic boys who, on growing up to be psychiatrists remain blandly optimistic about the environment and unconvinced of the role of faulty inheritance? Well, I doubt if he was—he was wiser than the quarrel between the inherited and the experiential in psychiatry. Had he forgotten for the moment (though none knew of it better than he) the irresistible drive experienced by most doctors to be always changing people? Or—and this is the likeliest explanation—being a psychoanalyst he may not have had many defective patients lately. I replied that it would be an extraordinary mother who would agree to let her backward baby remain untreated, if she suspected treatment existed. And it would be an extraordinary physician who would not try the treatment (after it had been sufficiently brought to his notice on blotters in the morning post) and present his cases at the local clinical meeting.

Another metabolic variety of idiocy, cretinism, has been treated enthusiastically, though with variable results, since the introduction of thyroid preparations. I told him that there was no reason to think that our descendants would not be equally enthusiastic about treating phenylketonuria.

Colleague No. 2, whose opinion I sought, censured what he called an ironical, and even *ingenious* tone in these reflections. He said he smelt emotion, and not scientific impartiality as became a psychiatrist. He suspected that I was trying to reform a situation which did not yet exist. There must have been some justice in this; it hurt a little.

The medical or amateur geneticist has a sad dilemma. The physicians he buttonholes are often resentful or frankly incredulous that the face of medicine could change in the manner he suggests. The geneticists he buttonholes do not doubt this in the least, and are good enough to look perturbed about it, but are apt to be pained by his hearty plumbing of the depths of the human genetic pool.

Both parties must pardon the present amateur geneticist if, to illustrate the situation under discussion, he extends the metaphor of the human genetic pool. Let us say that out in its misty centre an oncoming tidal wave has been discerned. Is it possible to be impartial about tidal waves, to study the phenomena, with scientific detachment, from a comfortable chair on the beach? This position has disadvantages, even in the case of small and comparatively playful tidal waves such as phenylketonuria.

Physicians are going to stay on the beach anyway, ignoring the geneticists yelling on the cliff-top. In the case of a really masterful tidal wave, or succession of tidal waves (to mention schizophrenia only) this position may be as tenable as any other.

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