The relevance of haemophilia's history to the broader story of how genetics became medical and medicine genetic runs against the grain of the standard narrative among practitioners of genetic medicine that stresses that medical genetics had very limited clinical relevance in therapeutic terms before the molecular turn of the 1980s and 1990s made gene-based interventions a promising and occasionally effective tool in the clinicians' therapeutic armamentarium. Among haemophilia specialists, specifically, the late 1980s and 1990s witnessed the first truly promising therapeutic applications of molecular biology in the form of recombinant DNA clotting factor concentrates. Yet as I have suggested in this essay, leading experimental haematologists had long regarded haemophilia as both a haematological and a genetic disease, and they had not only imagined these dimensions of the disease as complementary, but long viewed effective clinical management of the disease in terms of both heredity and blood. On the basis of what other historians of science and medicine are now uncovering, I suspect that haemophilia was not unique in this regard. In any case, it seems dubious today to call haemophilia 'the most hereditary of all diseases'; it is merely one among many prominent hereditary diseases in medical history that illustrates the actual as well as potential clinical rewards of explicitly framing medicine as genetic and genetics as medical.

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13 HOW PKU BECAME A GENETIC DISEASE

Diane B. Paul

The problematic of this essay may strike some readers as odd. After all, phenylketonuria, or PKU as it is more commonly known, was understood to be inherited nearly from the time it was first identified as a disease entity by Norwegian physician and biochemist Asbjørn Følling in 1934. Indeed, by the mid-1940s its autosomal recessive pattern of inheritance had been well confirmed. But the genetic aetiology of PKU was not always a defining characteristic of the disease. Whether an inherited condition is characterized as 'genetic', and, if so, the meaning and importance attached to that designation, is context dependent, varying with place, time, the specific features of the disease that are of greatest salience to patients, researchers and clinicians, and the general visibility of genetics in the culture. Thus Jean-Paul Gaudillière has shown that for Lionel Penrose and his British peers, the characterization of Down syndrome as a genetic (chromosomal) abnormality had very different implications than it did for Jérôme Lejeune and many of his compatriots in France.[1] And writing of cystic fibrosis, Keith Wailoo and Stephen Pemberton explain that in the 1960s and 1970s, 'neither families nor experts emphasized the "genetic" features of the disease. To be sure, they understood it to be a "hereditary" disorder, but this way of thinking did not capture what they saw as its fundamental biological underpinnings'.[2] This essay asks: when and why did the inherited nature of PKU come to seem a crucial feature of the disease, and with what consequences? Before tackling this cluster of questions, it might be useful to take note of a few essential facts about the nature of the metabolic error in PKU and how it is diagnosed and treated.

The Nature, Diagnosis and Control of PKU

PKU is a rare autosomal disorder of phenylalanine metabolism. Phenylalanine, an essential amino acid that is found in all dietary proteins, is necessary for protein synthesis and other biological functions. Because humans do not synthesize it endogenously, they must obtain it from the foods they eat. However, only some of the ingested phenylalanine is necessary for normal growth and development, with the rest ordinarily converted to another amino acid, tyrosine. In PKU, a

deficiency of the hepatic enzyme phenylalanine hydroxylase (PAH) results in an insufficiency of tyrosine and, more importantly, an excess of phenylalanine. In some way that is still not well understood, the accumulation of phenylalanine and its metabolites damages the developing brain. Before newborns were routinely screened for the disease, affected children typically experienced profound cognitive impairment and often other abnormalities, including small head size, hyperactivity, seizures and behavioural disruptions. In severe cases, children might lose interest in their surroundings and never learn to talk, walk, sit up by themselves, or control their bowels or bladder. Most such children were eventually institutionalized.

As early as the 1930s it was hypothesized that since humans only obtain phenylalanine from the foods they ingest, the effects of the disease might be ameliorated if affected infants were placed on a diet from which most of the phenylalanine was eliminated. This goal could not be achieved simply by avoiding dietary protein, since the result would be severe malnutrition. (Lionel Penrose had tried this approach in the 1930s with disastrous results.[3]) However, in the 1950s researchers succeeded in developing amino acid mixtures from which the phenylalanine had been removed through a charcoal filtering process, and experiments seemed to indicate that nutritional therapy could at least ameliorate some symptoms of the disease. Those experiments converged with the development of a urine test that could be used to detect the disease in infants, and some physicians, hospitals and public health programmes in the USA, UK and elsewhere began to screen asymptomatic newborns. But screening really took off in the 1960s with the invention by Robert Guthrie and his assistant Ada Susi of a bacterial inhibition assay for PKU that was simpler, cheaper and far more sensitive than the urine test, and that could administered just a few days after birth, before brain damage had occurred. At least equally important was the choice of blood – obtained by sticking the heel of the newborn – as the analyte. Unlike urine, blood is highly stable, making it possible for results to be sent to central laboratories where they could be processed in batches. By 1965 thirty-two American states had enacted screening laws, and by the end of the decade, blood spot screening for PKU had become routine in most US states and Canadian provinces, the UK, Australia, New Zealand, Israel, France and Germany. By the mid-1970s the practice was near universal in Central and Northern Europe.

As a result thousands of children and their families have been spared the devastating effects of this disease. Today many individuals who once would have been institutionalized can attend school, hold jobs, and marry and raise families. But the dietary regimen is arduous. A typical adult ingests about 3,500–5,100 mg of dietary phenylalanine each day. Adults with PKU are ordinarily advised to ingest no more than about 350–500 mg, and those with the most severe forms of the disease even less. To achieve a reduction on the scale suggested even in moderate cases requires not only the exclusion of obvious high-protein foods like meat, fish, nuts and dairy products, but also severe restrictions on such staples as wheat flour, rice (one-half cup cooked: 59 mg), pasta (one-quarter cup cooked spaghetti: 103 mg), potatoes and beans. Even many fruits and particularly vegetables contain substantial amounts of phenylalanine. For example, a medium banana contains 58 mg, a single medium Portobello mushroom 64, a quarter cup of raw peas 73, and a quarter cup of cooked spinach 164.[4] One plain bagel or a single slice of cheese pizza would exceed the total daily phenylalanine allowance for most people with PKU. Although there are low-protein substitutes for wheat flour, rice, pasta, bread and other food items, high manufacturing costs and small markets combine to make these products expensive, the costs are often not covered by insurance, and these artificial foods do not have either the consistency or taste of their natural counterparts.

Moreover, to ensure sufficient protein intake as well as calories, therapy for PKU must include substantial amounts of a special 'medical food' or 'formula' that contains all the necessary amino acids except phenylalanine, plus extra tyrosine, calories and often vitamins and minerals. The formula consists of free amino acids, which in contrast to intact proteins have an unpleasant taste and smell. To avoid large fluctuations in blood phenylalanine, the formula should be consumed in at least three servings spaced roughly evenly throughout the day.

In the 1960s, when blood screening for PKU began, it was generally assumed that the diet could be discontinued around the age of five, when gross brain development was complete. In reality, the need for treatment turned out to be perpetual. Controlling the phenylalanine intake of infants and small children, whose diets are largely determined by others, is a very different matter than it is for older children, and especially adolescents and adults, who make their own choices and who need to cope with the challenges of managing diet in the context of school, work and social activities. Food is central to the way we develop and maintain social relationships, but the extraordinarily restrictive PKU diet creates profound barriers to sharing meals with others. The diet is onerous for other reasons as well. People with PKU must calculate the phenylalanine content of everything they eat and factor it into their daily allowance. They can never be spontaneous about going to restaurants or to a friend's house for dinner. The medical food and low-protein substitutes are costly; the costs may not be covered by insurance, or if so only for children, up to a certain amount or with other limitations. For these and other reasons, few adolescents and adults rigorously adhere to the diet.[5] The multiple obstacles to adherence to the diet help explain why people with PKU often experience neuropsychological deficits, such as difficulties concentrating and generalized anxiety, and why they are twice as likely as their peers to experience problems in school.[6]

PKU as Paradigm

Nevertheless, dietary treatment for PKU has indisputably been a success, even if, as with many medical accomplishments, it is incomplete. That success has come to serve as the premier illustration of the point that 'genetic' should not be equated with 'fixed'. A typical example: 'There is a tendency among the lay public to believe that genetic means unchangeable. This belief is false. For example, the invariably serious neurological effects of phenylketonuria ... can be largely prevented by providing the affected newborn with a phenylalanine-restricted diet'.[7] In particular, the case of PKU has come to serve as a model of successful intervention in the course of a genetic disease. Indeed, it is often referred to as a paradigm for thinking about such diseases. Thus the Canadian biochemical geneticist Charles Scriver writes that '*PKU is now celebrated as one of the first human genetic diseases to have an effective rational therapy*. Such recognition constituted a "paradigm shift" in medical thinking about genetic disease in general'.[8] Today, in the discourse of biomedicine, the successful alteration of the course of PKU is used to illustrate the unique contribution of genetic research to the improvement of clinical outcomes and also to legitimate the expansion of newborn screening to other conditions and of other kinds of genetic testing. As British geneticist Angus Clarke notes, the PKU case has 'accumulated a large store of goodwill and of ethical credit in favour of genetic screening programmes' in general.[9]

However, before PKU could serve these purposes, the fact that it was *inherited* had to be emphasized to a much greater degree than had been the case in the 1960s, when most state screening programmes were established. To those politicians, parent advocates and others involved in the campaign to legislate screening for the disease, its hereditary character was of little importance. Similarly, while popular articles almost always noted that the disease was hereditary and occasionally described its recessive mode of transmission, the focus was elsewhere: on the ability to prevent mental retardation, thus sparing parents suffering and saving taxpayers money, and the possibility that a similar approach would prove effective against other retarding disorders. That the devastating effects of the disease had far more salience than its aetiology is reflected in the US state legislative hearings on mandated testing, where the fact that PKU was inherited received virtually no attention. None of the US statutes establishing newborn screening programmes even mentioned genetics. A committee that analysed the passage of those laws concluded that at the time, 'There was little recognition of the implications for public policy, or for the impact on individuals who were screened, of the fact that PKU is a *genetic* disease'.[10]

However, in the period when most US newborn screening programmes were established, the implications of that fact would anyway not have been obvious. A majority of US states had launched programmes by 1965, before prenatal diagnosis for the disease existed.[11] The PAH gene was only cloned in 1983, and in any case, access to abortion was highly restricted in the 1960s. PKU testing did incidentally provide information on carrier status since the parents of affected infants would be obligate heterozygotes. But in the 1960s the question of what difference it might make, if any, that a disease was genetic – and associated issues of genetic discrimination, confidentiality and privacy – did not yet appear on the policy agenda. (That is one reason for the lack of informed consent requirements in most newborn screening programmes.) These issues would only emerge in 1970s as the result of developments in both molecular and medical genetics.

Genetics in the Wider Culture: The 1970s

The mid-1970s witnessed an explosion of controversy over the use and regulation of genetic technology. One catalyst was the advance in molecular biology, which, even before the development of recombinant DNA (rDNA) techniques, prompted predictions of the 'genetic engineering' of new genes and human qualities. Already in 1969, California Institute of Technology molecular biologist Robert Sinsheimer eagerly anticipated the emergence of a 'new eugenics' that would overcome the limitations of the old variety. In his view, attempts to manipulate human breeding, a slow and clumsy process, would soon be replaced by direct genetic interventions – a prospect applauded by some commentators and deplored by others.

Then in 1973 Herbert Boyer and Stanley Cohen created the first transgenic organism by splicing frog DNA into a plasmid for an *E. coli* bacterium, an achievement followed a year later by Rudolf Jaenisch's creation of the first transgenic animals with the introduction of a foreign DNA tumour virus into the genomes of mice. The rapidly increasing ability to join molecules from diverse sources generated concern as well as excitement among elite molecular biologists, several of whom warned of the possibility that recombinant organisms of an unpredictable nature could be created and prove harmful to laboratory workers or, should they escape from laboratory containment, the general public. Their calls for strict procedures to prevent escape from containment and a moratorium on very risky experiments culminated in the Asilomar Conference of February 1975, which produced a temporary consensus that there should be extreme caution in rDNA experiments. Concern soon expanded beyond the boundaries of the molecular biology community. The US Congress held hearings on rDNA research, and some localities implemented their own regulations. Whether the new technology presented a threat to health or the environment or would serve to revive eugenics became matters of intense public concern. With the rapid commercialization of the field, debates also swirled around the morality of 'patenting life'.[12]

Contemporaneous developments in medical genetics aroused a similar mix of enthusiasm and concern. Amniocentesis, the first practical method for detecting genetic disorders in pregnancy, was developed in the 1960s but was of little practical utility before abortion was decriminalized. Following passage of the 1967 Abortion Act in the UK and the 1973 US Supreme Court decision in *Roe v. Wade*, amniocentesis for the purpose of detecting Down syndrome increasingly became a routine aspect of clinical practice. But the use of prenatal diagnosis also provoked controversy, especially around the issue of whether policies designed to forestall the birth of affected children signified a new eugenics.

In the 1970s as well, national and state legislation was first enacted to support research on genetic diseases, as well as promote and regulate genetic screening programmes. Responding to pressure from black professionals, celebrities and community activists who argued that the incidence of sickle cell anaemia was much higher than that of diseases that received far more attention, and that the neglect was explained by the race of the sufferers, in 1972 the US Congress passed the National Sickle Cell Anemia Control Act, which provided funding for sickle cell research, educational activities, and screening and counselling programmes. In his signing statement, President Richard Nixon declared sickle cell anaemia to be an 'especially pernicious disease because it strikes only blacks and no one else'.[13] Four years later Congress enacted the National Sickle Cell Anemia, Cooley's Anemia, Tay-Sachs, and Genetic Diseases Act, which permitted public funds to be used for voluntary genetic screening and counselling programmes.

By the mid-1970s many screening programmes (under a variety of public and non-governmental auspices) had been established for sickle cell disease and carrier status and also, at the community level, for Tay-Sachs disease. As there was no effective treatment for either disease, the primary aim of such screening was necessarily to provide reproductive information. But sickle cell testing was soon engulfed in controversy when widespread confusion between the sickle cell trait and the disease sickle cell anaemia resulted in the stigmatization of carriers and sometimes discriminatory treatment in jobs and education.

PKU Screening as a Cautionary Tale

In this context of heightened awareness of potential pitfalls in screening for genetic conditions, the question arose of what could be learned for the development of other screening programmes from the relatively extensive experience of screening for PKU. The Committee on Inborn Errors of Metabolism of the National Academy of Sciences (NAS), chaired by distinguished paediatrician and geneticist Barton Childs, was charged with investigating the history, current standing and effectiveness of screening for PKU, and also with reviewing screening programmes for other genetic conditions such as the haemoglobinopathies (sickle cell disease and trait and Thalassemia) and Tay-Sachs disease.

In its 1975 report the committee concluded that PKU screening was justified, but it criticized the haste with which screening statutes were enacted in the mid-1960s when there existed unanswered questions regarding which infants needed to be treated and for how long and the efficacy of the low-phenylalanine diet. According to the report, 'mass screening and treatment were implemented on a broad scale before adequate data were available on the indications and necessity for such treatment', and the decision to mandate the test was characterized as 'ethically questionable because of failure to consider enough facts'.[14] Legislators, hoping to save money and responsive to intense pressure from local parent organizations, enacted statutes whose implications they did not fully understand. To avoid a repetition of this experience, there should be greater oversight of genetic screening programmes, and the committee proposed a set of ethical, legal and economic principles to govern their operation.

The history of newborn screening for PKU thus served as a cautionary tale for genetic testing in general.[15] The lesson drawn by the committee and other commentators was that genetic tests should be assessed by more stringent criteria than was applied in the case of PKU, where screening was mandated prematurely, with 'thousands of infants ... subjected to an incompletely validated and potentially hazardous intervention'. The point was that although we were lucky and narrowly dodged the bullet, we cannot count on being so fortunate and should not make that mistake again.[16] But history could only serve as a warning if the Guthrie-Susi bacterial assay was defined as a genetic test and the uncertainties, complexities and unintended consequences of screening and treatment for the disease emphasized.

However, in other contexts of genetic research and medicine, the PKU story was already taking a different and ultimately more consequential turn, one that would reinforce the geneticization of the disease but also result in a radical simplification of the account of life with the disease. That trend began in the 1970s with the controversy over the genetics of intelligence and intensified in the 1980s with the debates about whether to map and ultimately sequence all human genes.

PKU and the Critique of Genetic Determinism

In 1969 Berkeley psychologist Arthur Jensen famously asked: 'How much can we boost IQ and scholastic achievement?' His answer, in effect, was 'not much'. According to Jensen, genetic differences accounted for at least half of the black-white gap in IQ test scores, which explained why compensatory education schemes had failed.[17] His essay produced a storm of controversy, with Jensen criticized both for exaggerating the significance of heritability estimates and for inappropriately generalizing from statistics on the heritability of IQ differences within races to conclusions about differences between them. Two years later Harvard psychologist Richard Herrnstein published an analogous argument in respect to social class, which he soon expanded to a book, *I.Q. in the Meritocracy*.[18]

The IQ debate had initially focused on the validity of genetic explanations for group differences in intellectual performance. The heritability of *individual* differences was taken for granted. Studies published by British psychologist Cyril Burt had seemingly established a heritability of about 80 per cent for IQ. But in 1972 Princeton psychologist Leon Kamin charged that Burt's results were, statistically speaking, too good to be true. After reviewing Burt's and the four other classic studies of the heritability of IQ, Kamin concluded that, 'there exist no data which should lead a prudent man to accept the hypothesis that I.Q. test scores are in any degree heritable'.[19] A heated debate followed on both the standards required to demonstrate the heritability of intelligence and the scientific and social value of heritability estimates.

Proponents of such research argued that it was both possible and desirable to design experiments on the heritability of human cognitive and personality traits, including intellectual performance, that met 'reasonable' methodological criteria; that newer and better-designed studies had confirmed the existence of a substantial heritability of IQ, even if the new estimates were lower than Burt's; and that these results mattered for social policy. The message was typically that compensatory education and other policies designed to overcome the effects of poverty and racism have rested on a naive belief in the power of the environment; to succeed, interventionist strategies needed to take genetic differences (as reflected in heritability estimates) into account. Critics, on the other hand, generally argued that heritability estimates of human mental and behavioural traits were scientifically and socially meaningless. They stressed the methodological difficulties involved in designing experiments that would break the association of genotype and phenotype (a problem resulting from the fact that relatives generally share similar environments), and they insisted that the enormous efforts required to overcome this problem could not be justified by either the potential scientific or social interest of the results. Heritability estimates, they argued, lack any policy relevance since they are not a measure of the importance of genes in determining an individual's phenotype; they are not generalizable (since heritability estimates vary with the mix of populations and environments); and above all, they are not an index of plasticity.

In the context of this emotionally charged debate, the efficacy of treatment for PKU provided a dramatic, decisive and easily understood rejoinder to the argument that a high heritability of IQ would defeat efforts to boost scholastic performance. Critics stressed that PKU was a trait with a heritability of 1.0; that is, all the phenotypic variation among newborns is due to genetic variation. Yet an environmental intervention prevents otherwise severe neurological damage. The ability to intervene in PKU thus demonstrates that a trait may have a high heritability and still be extremely sensitive to environmental change. Because the PKU case provided such a clear illustration of the fact that biology is not destiny,

it came to serve as the standard illustration of the flaws of genetic determinism. In the early 1970s critiques of Jensen and Herrnstein almost invariably invoked the ability to intervene in PKU in arguing that research on the heritability of IQ was misguided. Indeed, the editors of a 1976 compendium of critical readings on the IQ debate wrote, 'To use the standard example, consider phenylketonuria', in explaining how novel manipulations of the environment can not only improve the performance of a given population (in the PKU case, the IQ scores of treated children) but reduce individual differences as well (since the diet would raise the mean IQ of children with the disease but not of others).[20]

A few years later, when the sociobiology debate erupted, the case of PKU was again deployed to argue against genetic determinism. The following passage from a contemporaneous critique is typical:

> There is an allele that, on a common genetic background, makes a critical difference to the development of the infant in the normal environments encountered by our species. Fortunately, we can modify the environments ... and infants can grow to full health and physical vigor if they are kept on a diet that does not contain this amino acid. So it is true that there is a 'gene for PKU'. Happily, it is false that the developmental pattern associated with this gene in typical environments is unalterable by changing the environment.[21]

The same example was again invoked for the same purpose when the IQ debate re-emerged with the 1994 publication of Richard Herrnstein and Charles Murray's *The Bell Curve*, which argued that intelligence is highly heritable and that differences in intelligence largely explained individual and group differences in social and economic status in the USA. Like Arthur Jensen, the authors also maintained that environmental interventions to raise IQ scores had proved largely futile, and that to be successful, social policy needed to take facts about the genetics of intelligence into account. The debate resurrected all the arguments and counter-arguments of the 1970s, including the same use of PKU. For example, one trenchant review of *The Bell Curve* argued that its authors were wrong to conclude that 'equalizing environments will have no effect' on intellectual performance, for 'it turns out that if you put all infants on a diet low in the amino acid phenylalanine, the disease disappears'.[22]

PKU and the Human Genome Project

While critics in the sociobiology and IQ debates cited PKU to argue that the social order is 'not in our genes', others deployed PKU for a quite different and in some ways contradictory purpose: the defence of a genetic approach to medicine, and particularly the international effort to map and sequence the complete human genome. When the Human Genome Project was first proposed in the mid-1980s, many biologists expressed concern that it would siphon funds from

other, more scientifically interesting efforts. Potential funders were also wary. Aiming to convince their peers, members of Congress and the general public that this expensive project represented a worthwhile expenditure of public money, proponents mounted an intense public relations campaign that involved expansive claims for the scientific, technological, economic, social and medical value of the project. The information gained would secure US leadership in biotechnology and promote economic competitiveness, produce technologies that would revolutionize many domains of biology, and generate 'deep insights into the nature of humanity and our relationships to the world of which we are a part'.[23] Above all, it would alleviate suffering. Thus, according to its supporters, the project would revolutionize medicine, resulting in cures for dread diseases – an aim with deep appeal to Congress. According to Harvard molecular biologist Walter Gilbert, a 1980 Nobelist in chemistry, co-inventor of a major technique for DNA sequencing, and co-founder of the biotech companies Biogen and Myriad Genetics: 'The possession of a genetic map and the DNA sequence of a human being will transform medicine'.[24] Biologist Leroy Hood, inventor of an instrument to automate DNA sequencing and co-founder of several biotech companies, agreed that 'access to the genetic and sequence maps will fundamentally change the practice of clinical medicine'.[25]

But *why* should it revolutionize medicine? The assumption was that locating disease-causing genes on chromosomes and determining their nucleotide sequence was requisite to a deep understanding of the causes of disease and hence to the development of truly effective interventions. As James D. Watson, first director of the project, explained in summarizing a conversation with a congressman, in the struggle against disease it is an enormous advantage to find that genetics is a contributing cause. 'Ignoring genes is like trying to solve a murder without finding the murderer', he claimed. 'All we have are victims'. According to Watson, 'if we find the genes for Alzheimer's disease and for manic depression, then less money will be wasted on research that goes nowhere'. We thus need to convince members of Congress 'that the best use for their money is DNA research'.[26]

Critics were unimpressed by such claims for the importance of genomic information for human health.[27] They maintained that the project advocates were overpromising, and typically cited the 'therapeutic gap' – the fact that genetic research had produced many more tests to diagnose or predict disease than means to effectively treat or prevent it, except by preventing births of affected individuals. They noted that 'causal stories are lacking and therapies do not yet exist; nor is it clear, when actual cases are considered, how therapies will flow from a knowledge of DNA sequences'.[28] They tended to be especially sceptical of promises that gene therapy aimed at curing rather than mitigating the symptoms of disease would follow from possession of mapping and sequencing data.

In the context of controversy over the genome project, the PKU story acquired immense appeal to geneticists. With few effective interventions to point to other than abortion, the success in treating PKU came to function as a standard rejoinder to critics of the project, and more generally as a way to legitimate both genetic research and the expansion of genetic testing. Already in the early 1980s a metabolic clinician-researcher had remarked that neonatal screening programmes for PKU 'have been widely cited in textbooks of biology and genetics and in lectures to the general public', since they represent 'one victory in the struggle against genetic factors, which are seen as being unalterable'. And he noted that 'PKU programs have become a showcase of the benefits to be derived from large-scale screening for genetic disorders'.[29] With the controversy over the genome project, the case of PKU acquired even greater value to advocates of a genetic approach to medicine in general, and the expansion of genetic testing in particular.

The legitimating role of PKU is nicely illustrated by a pair of National Public Radio (NPR) interviews conducted in the 1990s. In the first, a caller to a show on the Human Genome Project asked about the relevance of genomics to breast cancer. He noted that the popular press was full of stories 'about the magic of science and how genes are going to solve all of our problems', suggested that we should focus more on social context, and asked, 'Has anything ever been solved by genetic research?' His question was tackled by Robert Waterston, director of the Genome Sequencing Center at the Washington University School of Medicine, who replied: 'In terms of has it solved anything, there's a genetic disease called phenylketonuria – PKU – and just simply by testing infants at birth – and for those infants who test positive, if you give them a different kind of milk, you prevent brain damage. So this is clearly an instance'.[30] Three years later, Francis Collins, then director of the US Human Genome Project, was also interviewed on NPR. That interview was bookended by comments on PKU. At the beginning, after acknowledging that 'the clinical consequences of genetics have been largely in the diagnostic arena up until now', Collins stressed that there are also genetic diseases for which treatments have been developed, 'including the one that all newborns are screened for, the thing called PKU, where simply getting on the right diet prevents mental retardation'. At the close, responding to a question about BRCA testing, he replied: 'I would say lives have been saved from this sort of genetic effort, actually, extending back some 20 or 30 years. And again, PKU is the example where the paradigm was proven'.[31]

A Triumph for Genetic Research?

For PKU to legitimate the Human Genome Project, the success of screening had to be attributed to a 'genetic effort'. But screening and treatment for the disease had been routinized in North America and much of Europe two decades before

the PAH gene was cloned. The ability to treat PKU rested on the biochemical insight that an excess of dietary phenylalanine was somehow connected to the mental retardation associated with the disease, and that the symptoms might thus be mitigated if exposure to phenylalanine were reduced – an insight dating back to the 1930s. The attribution of the ability to prevent mental retardation to *genetic* research is a product of the 1980s and the controversy over the genome project. But it has now become standard, repeated even by those with no stake in promoting a genetic approach to medicine. For example, under the heading 'Most Traits are Affected by Environmental Factors as well as by Genes', the authors of a well-respected genetics textbook write that as a result of dietary treatment, the capacities of children with PKU 'can be brought into the normal range', and that 'PKU serves as an example of what motivates geneticists to try to discover the molecular basis of inherited disease. The hope is that knowing the molecular basis of the disease will eventually make it possible to develop methods for clinical intervention through diet, medication, or other treatments that will ameliorate the severity of the disease'.[32]

Improved molecular understanding may well enable more effective or less burdensome clinical interventions in PKU. But to date genetics has contributed remarkably little to either diagnosis or therapy for the disease. Both carrier testing for at-risk relatives and prenatal diagnosis for pregnancies at increased risk are possible if the specific disease-causing mutations in the family have already been identified, but the required analysis is complex and expensive, and neither procedure is widely used.[33] The cloning of the PAH gene generated enormous excitement about the prospect of gene therapy – but as with gene therapy more generally, those hopes were eventually disappointed.

Mutation analysis is sometimes helpful in predicting the severity of disease and in tailoring individual treatments. There is great allelic variation in PKU, however, with over 500 mutations identified in the PAH gene, and most individuals with the disease are compound heterozygotes.[34] This complexity has hampered efforts to develop diagnostic procedures based on genotype-phenotype correlation.[35] In treating patients, it may be useful to know whether a particular mutation is mild, moderate or severe. In particular, genotyping may help predict which individuals will respond to a new therapy involving supplementation with sapropterin (otherwise known as BH4 or by its trade name, Kuvan), an enzymatic cofactor for phenylalanine hydroxylase. But these are recent developments. To claim that the prevention of brain damage in PKU is a clear instance of 'genetic research' mocks the historical record.

As PKU acquired symbolic meaning, the story of its diagnosis and treatment became progressively simpler. Its cultural transformation began with the IQ and sociobiology controversies, where it served to illustrate what was wrong with genetic determinism, and it intensified with the controversy over the Human

Genome Project, where it served to demonstrate the value of a genetic approach to medicine in general and to the expansion of genetic testing in particular. Of course it functioned most effectively for these symbolic purposes when shorn of complications. In the 1960s and 1970s uncertainties, mistakes and unintended consequences were widely acknowledged, at least among medical geneticists and professionals in public health. But as PKU acquired paradigmatic status, all nuances were lost. 'One can, in fact, have the gene, yet with proper dietary changes never show the manifestations', writes one author.[36] According to another, by limiting dietary phenylalanine, 'individuals with the two mutant alleles for processing phenylalanine can avoid the toxic buildup of the amino acid in their brain. In essence, they modify their environment so that it contains little or no phenylalanine. And in that environment, the PKU mutant alleles are harmless'.[37] In the now ubiquitous narrative, treatment appears effortless and the cure complete. Individuals with PKU and their families and clinicians could only wish that were so.

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HUMAN HEREDITY IN THE TWENTIETH CENTURY

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