MEDICINA NEI SECOLI ARTE E SCIENZA, 14/3 (2002) 773-791
Journal of History of Medicine

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CONTESTED CONCEPTIONS: PKU IN THE POSTWAR DISCOURSE ON REPRODUCTION

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SUMMARY

This essay uses the case of PKU as a portal through which to view shifting and contested views about genetics and reproductive behavior. In the early 1960s, the development of an effective therapy for PKU converged with the development of a test that could reliably detect the condition in newborns. As a result, infants born with the condition were enabled to reach adulthood and reproduce. However, by the early 1980s, a "second-generation" effect of screening was manifest, whereby many infants born to women who had been salvaged by screening were themselves severely damaged. In the 1940s, Lionel Penrose employed the case of PKU to demonstrate what was wrong with eugenics. Twenty years later, it would be used to illustrate why controls on reproduction were needed.

Introduction

At the 1968 dedication of the new Mount Sinai School of Medicine, British immunologist Sir Peter Medawar joined American biochemist Linus Pauling in urging carriers of severely deleterious recessive genes to restrict their reproduction. Medawar invoked the case of phenylketonuria or PKU, an autosomal recessive "inborn error of metabolism" then assumed to have an incidence in Britain and the U.S. of about 1 in 20,000—25,000 individuals. In PKU, a defective gene results in an inability (or greatly reduced ability) to metabolize phenylalanine, an essential amino acid found in all dietary protein. Phenylalanine is ordinarily converted to another amino acid, tyrosine, but

Key words: Phenylketonuria - Maternal phenylketonuria - Mental retardation

in PKU, it accumulates to toxic levels in the blood and tissues, often causing drastic neurological damage, and subsequent physical and behavioral abnormalities, including severe mental retardation. In 1960, a simple and reliable test to detect PKU in newborns was invented. Within a decade, screening for the condition had become routine in much of the US and Britain. Infants found to be affected were placed on a restricted diet from which most of the offending amino acid had been removed. Those who received prompt treatment were spared the worst sequelae of the disease, in particular, the mental retardation.

Nevertheless, in his 1968 talk, delivered after screening and treatment had become commonplace, Medawar asserted that carriers for the gene for PKU "should be discouraged from marrying each other" on the grounds that, on average, half their children would also be carriers, while a quarter would be affected. The idea that everyone had a right to reproduce seemed to him absurd. "It is humbug to say that such a policy violates an elementary right of human beings," Medawar asserted. "No one has conferred upon human beings the right knowingly to bring maimed or biochemically crippled children into the world." But even if carriers refrained from marrying each other, the problem would not be solved, for if they married "normals," the result would be a steady increase in the frequency of the offending gene. "We are dealing here with a genetic equivalent of inflationary economics," he explained, for "we seem to be getting on all right, but the currency is deteriorating"[1].

Medawar's remarks may have been prompted by the presence of his fellow Nobelist Pauling, who had long warned of the threat of genetic deterioration. Like the geneticist H.J. Muller, who strongly influenced his views on the matter, Pauling believed that exposure to ionizing radiation, combined with advances in medicine, was dangerously increasing the human mutation rate. "The human race is deteriorating," Pauling had warned in 1959. "We need to do something about it"[2]. Unlike Muller, whose anticommunism was even stronger than his fear of the genetic damage from radiation, Pauling vigorously campaigned to end atmospheric nuclear testing. He also departed from Muller on the desirability of positive eugenics. In 1959,

Muller revived a much earlier proposal to bank the sperm of particularly accomplished men in hopes that some prospective parents who were fertile would voluntarily chose artificial insemination. But Pauling feared that "germinal choice" (as Muller's revised proposal was known) would ultimately result in fewer contemplative intellectuals and more social conformists. On the other hand, he considered negative eugenics eminently sensible, since "no objection can be legitimately raised...against the ambition to eliminate from human heredity those genes that lead to clearly pathological manifestations and great human suffering"[3]. In fact, Pauling considerably outdid Muller in his proposals to control reproduction.

In Pauling's view, couples with a defective child should stop having children since even if their offspring were normal, they would be carriers of genes that cause suffering. Thus the law should require testing of all individuals in communities where the incidence of genes for particular molecular diseases is high[4]. Carriers should then refrain from marrying each other or having biological children. In a 1968 essay, Pauling famously proposed that legislation be adopted to require every young person to have tattooed on their forehead symbols for any seriously defective recessive genes, such as those for sickle-cell anemia and PKU, so that they would refrain from falling in love with each other—a proposal he reiterated at Mt. Sinai[5]. Like Medawar, he realized that such a masking strategy would do nothing to decrease the incidence of the defective gene. Therefore, he thought that carriers who marry noncarriers should have a lower than average number of offspring.

Why would Medawar and Pauling both warn in 1968 of the long-term threat represented by an increase in the incidence of rare recessive genes? And why would they (and others) employ the case of PKU to illustrate their point? How has thinking about the meaning of PKU changed since the 1960s, and what does this transformation tell us about changing norms concerning reproduction? In 1946, Lionel Penrose explained that he chose to focus on PKU as the subject of his inaugural address as Galton Professor of Eugenics at University College, London partly for the intrinsic interest of the condition and "partly be-

cause it demonstrates many of the problems of eugenics as they appear in the light of recent knowledge"[6]. As this essay shows, PKU continues to exemplify the problems of eugenics—or more precisely, the issue of whether particular reproductive choices can ever be wrong.

The historical context

The passages from Medawar and Pauling are jarring to contemporary sensibilities. Their basic assumption that procreative choices are ultimately social is one that today is rarely expressed, at least by opinion-makers. The current discourse on reproduction valorizes rights. Any suggestion that some choices are irresponsible would be branded eugenics, now assumed to be evil—even if state intervention were explicitly rejected. It is often assumed that talk of the need to restrict reproductive choices on behalf of the children-to-be, the larger society, and future generations disappeared after WW II. Although there was indeed a shift in thinking (or at least talking) about reproduction, the process of transformation was both slower and much more uneven than many seem to think.

Well into the 1970s, it was common for both scientists and theologians (the two groups then typically invited to pronounce on what now are termed "bioethical" issues) to assert that no one had the right to bring a disabled child into the world. One has only to examine the proceedings of the many conferences organized in the 1960s on the social implications of advances in genetics to see how varied at the time were beliefs about reproductive rights. These conferences tended to be dominated by scientists who generally shared the view that there was no blanket right to reproduce. But it is clear that they often felt (or at least presented themselves as feeling) beleaguered. Thus the point is not that the viewpoint of Medawar and Pauling was typical, for the 1960s is characterized by a cacophony of voices. It is rather that their view was quite respectable, especially among the rather narrow group of individuals whose opinions were solicited regarding the social implications of advances in genetics. A secondary point is that opponents of positive eugenics may still believe individuals have a responsibility not to transmit bad genes

or diseases. These points are well-illustrated by the debate between the two leading Protestant theologians of the time, the Episcopalian Joseph Fletcher and the Methodist Paul Ramsey.

The views of Fletcher and Ramsey are often counterpoised, for they seem to have disagreed about everything. Fletcher was a civil-rights and anti-Vietnam War activist, who marched and picketed for many liberal causes. Ramsey was a social conservative, who defended the war[7]. More relevant to our purposes, Ramsey was as skeptical as Fletcher was enthusiastic about the benefits of human "genetic engineering." Fletcher, the founder of "situation ethics," was like Pauling a utilitarian who judged the rightness or wrongness of acts by their consequences for human well-being. From this standpoint, he approved of contraception, abortion, sterilization, and euthanasia. Arguing that humans should aggressively take charge of their own evolution, he also applauded artificial insemination by donor, cloning, and every other actual or potential intervention that he thought might advance that end. "Man is a maker and selecter and a designer," he wrote, "and the more rationally contrived and deliberate anything is, the more human it is"[8] (a perspective reflected in the title of his 1974 book, *The Ethics of Genetic Control: Ending Reproductive Roulette*). Ramsey (as well as Leon Kass and the Jesuit theologian Richard McCormick) strenuously disagreed. In their deontological perspective, life was sacred, and abortion, euthanasia, and all the potential forms human genetic engineering inherently wrong.

But the emphasis on the very real disagreements between Fletcher and Ramsey has obscured the fact that both were sympathetic to negative eugenics. Thus Fletcher maintained that individuals at risk for transmitting severe diseases should not be allowed to reproduce. "The right to conceive and bear children has to stop short of knowingly making crippled children...just as the rights of parents have had to bow to required schooling and the rights of voluntary associations have had to bow, in public services, to the human need to be respected regardless of ethnic and racial differences"[9]. At least on that point, Ramsey agreed. In *Fabricated Man*, his 1970 critique of genetic engineering, Ramsey asserted: "Christian teachings have always held that by

procreation one must perform his duty to the future generations of men; procreation has not been a matter of the selfish gratification of would-be parents. If the fact-situation disclosed by the science of genetics can prove that a person cannot be the progenitor of healthy individuals (or at least not unduly defective individuals) in the next generation, then such a person's 'right to have children' becomes his duty not to do so, or to have fewer children than he might want (since he never had any right to have children simply for his own sake)." Indeed, Ramsey considered that the marriage licensing power of the state might be used to prevent the transmission of grave genetic defects. To those who might consider this an infringement of liberty, he replied that "the freedom of parenthood" is only the freedom of responsible parenthood and not a license "to produce seriously defective individuals"[10].

As noted, a number of respected scientists agreed. Thus Francis Crick asserted at a famous 1963 Ciba Foundation conference that we must "get across to people the idea that their children are not entirely their own business and that it is not private," a comment that prompted N.W. Pirie to remark that "in a society in which the community is responsible for people's welfare," the answer to the question of whether there is a right to have children is "No"[11]. Writing specifically of PKU, Sheldon Reed asserted that "no couple has the right to produce" a child with that condition[12].

In fact, many commentators thought they saw a trend. Ramsey for one was convinced that the future would see more, rather than fewer, proposals for reproductive control[13]. Similarly, medical geneticist Joseph Dancis remarked in 1973 on the growing sentiment "among both physicians and the general public that we must be concerned not simply with the birth of a baby, but of one who will not be a liability to society, to its parents, and to itself"[14]. In the same year, the author of an article in *Fortune* commented: "A good many geneticists hold that society ought to encourage parents to avoid giving birth to children crippled by such genetic ailments as mongolism." The article cited Cal Tech biologist James Bonner, who anticipated "the rise of 'a new morality' in which couples will say, 'Since we will have only two children, let them be free from genetic defects"[15].

But we might still be amazed to find Medawar joining the chorus. After all, he is considered a critic of eugenics. And indeed he was—in some respects, and at some times. Anyone whose knowledge of Medawar's views derived from the proceedings of the Ciba conference would surely see him as a critic. All of his comments, especially on Muller's sperm-banking proposal, are skeptical. He expresses reservations both about the ends and the means, arguing that we do not know enough about the inheritance of mental and behavioral traits to engage in a breeding program, and like Pauling, that we can not trust that the traits bred for will be good ones. Elsewhere, he stresses (a la Muller's most prominent critic, Theodosius Dobzhansky) that the degree of heterozygosity in humans implies that even if we could decide on a genetic elite, we could not count on it to breed true[16].

But these arguments all tell against positive and not negative eugenics. Medawar himself often opposed the two, asserting that by contrast with positive eugenics, the negative form "has the altogether lesser and more realistic ambition of diminishing, and as far as possible correcting, the distress caused by deleterious genes and genetic conjunctions." Even here, he sometimes appeared as a critic, arguing that sterilizing mentally deficient people would be ineffective, since most of the offending genes were hidden in symptomless heterozygotes, and that it would truly be a "night of the long knives" if we were to sterilize them[17]. He also noted that, conversely, the relaxation of selection against rare recessives (such as the gene for PKU) would only slowly increase their incidence, and that the genetic medicine of the future may be able to repair the damage. So he frequently denounced alarmists. But he also thought that claims for a right to reproduce were nonsensical. Writing in 1983, Medawar reiterated his earlier suggestion that PKU carriers should be discouraged from marrying each other, and noted: "To many, many people—especially those who have appointed themselves guardians of civil liberty and the conscience of us all—the idea that anyone should not marry whom he or she chooses is seen as a gross invasion of personal liberty, a wanton withdrawal of natural rights. This is a most questionable argument, for who has conferred upon human beings the right to bring genet-

ically crippled children into the world?"[19] Medawar truly exemplifies the point that the categories of "eugenicist" and "anti-eugenicist" are historical, with boundaries that change over time and are far from clear-cut.

Pauling's views may surprise for a different reason. Although Medawar (like Fletcher) was a political progressive, Pauling is famous for his active involvements in the peace and other social movements. He tirelessly promoted the causes of anti-militarism, anti-racism, and income redistribution. His guiding ethical principle was the reduction of suffering. From Pauling's own perspective, the anti-nuclear and other campaigns were of a piece with his negative eugenics. The difficulty we have in fitting these pieces together is reflected in the fact that biographies of Pauling mention the last in an embarrassed few paragraphs, when they mention it at all[20].

Why PKU?

We have seen that the comments of Medawar and Pauling on reproductive responsibility were not so extraordinary at the time. But PKU may still seem an odd choice of example. After all, the disease entered public consciousness in 1946 when Penrose used PKU to demonstrate a number of fallacies in eugenic thinking. In "Phenylketonuria: A Problem in Eugenics," he noted that because the condition is rare and recessive, the responsible genes are found overwhelmingly in the general population. The affected represent only the tip of an iceberg, and in any case rarely reproduce. A policy of eugenic sterilization against them would thus be doubly ineffective. To make substantial progress would require identifying and sterilizing the heterozygotes, an absurdly large number of people. Penrose assumed an incidence of PKU in Britain of 1 in 50,000, which implied (according to the Hardy-Weinberg principle) that 1 in 100 people would be carriers. "Only a lunatic," he asserted, would favor sterilizing 1% of the normal population "to prevent the occurrence of a handful of harmless imbeciles"[21]. Sterilizing the close relatives of those affected on the grounds that they were likely to be carriers would also leave untouched the large reservoir of offending genes in the general population, and would involve many mistakes.

Moreover, there are many rare recessive disabilities; Penrose surmised that about two in every three people was a carrier for some serious defect. Sterilizing only those who could be detected would therefore be arbitrary. Eugenically, the only practical course was to prevent inbreeding in affected families and, ultimately (as Medawar, Pauling, and earlier, J.B.S. Haldane suggested), discouraging matings between those who carried the same deleterious gene (thus denying "natural selection its legitimate prey"). Although doubtful that a cure was possible, Penrose also speculated that a medical approach to alleviating the symptoms of PKU might one day succeed. (He himself had unsuccessfully experimented in the 1930s with dietary therapy). That a condition is inborn does not necessarily imply that it is untreatable. After all, he noted, children with club-feet have been enabled to walk and those with cataracts to see — a precursor of the contemporary argument, for which PKU has become the exemplar, that "genetic" need not be equated with "fixed"[22].

Like Penrose, Pauling was also involved with PKU research. Although primarily associated with sickle-cell anemia, whose molecular basis he identified in a celebrated 1949 paper, Pauling's long-standing interest in mental disease, which he considered the most significant source of suffering in the U.S., prompted an interest in PKU. In 1955, he received a large five-year grant from the Ford Foundation for work on the biochemical basis of mental deficiency[23]. One goal of the project, consistent with Pauling's eugenic interests, was development of an intravenous phenylalanine tolerance test to identify heterozygotes for PKU, who could then "be warned not to marry other heterozygotes in order to avoid the birth of phenylketonurics"[24].

The main point of the work on PKU was to elucidate the mechanisms involved in the production of mental deficiency in phenylketonuria. At this time, Pauling was developing his theory of "orthomolecular psychiatry," according to which mental disease could be treated "by the provision of the optimum molecular environment for the mind, especially the optimum concentrations of substances normally present in the human body"[25]. Therapy for PKU, which involved limiting the supply of dietary phenylalanine in order to approximate the normal con-

centration of the amino acid and so alleviate the manifestations of the disease, was for Pauling a paradigmatic example of this approach.

In the 1950s, the prospects for therapy were limited by the lack of a reliable diagnostic test that could be administered soon after birth, before irreversible brain damage had occurred. That problem was solved in 1960, when microbiologist Robert Guthrie, who had a niece with PKU, developed a bacteriological test suitable for mass screening. The Guthrie test, which involved puncturing the heel of the newborn to obtain a blood specimen, was simple, sensitive, and inexpensive, and could be administered while the infant was still in the hospital, with the specimen sent to a central laboratory for testing. Announcement of the test generated enormous excitement and publicity despite the rarity of the disease, which made only a small contribution to the problem of mental retardation (accounting for less than one percent of institutionalized patients). At the time, it was widely assumed that many other disorders, including other forms of hitherto intractable mental retardation, would yield to the same basic strategy. Pauling, for example, was not interested in PKU in itself, but as a model for the treatment of mental disease more generally. The Ford Foundation-sponsored project was viewed by the Pauling team "as a wedge to open the door on more general studies of mental deficiency," and mental deficiency studies in turn as an opening wedge to studies of mental disease[26]. That the PKU control program represented a new paradigm for medicine was widely assumed. As Guthrie explained, it opened the door "to a whole new era of preventive medicine based upon a new understanding of medical genetics"[27]. That assumption was reiterated in numerous magazine and newspaper articles and even Congressional speeches calling for mandated use of the Guthrie test. It explains why the AMA, in its 1962 year-end report, hailed the test as a major medical breakthrough[28].

In 1963, Massachusetts required PKU screening of all infants in that state, and within a decade, screening had become routine (often mandated by law) in other states and many countries. Britain's national program was established in 1969. However, it should be noted that not everyone enthusiastically embraced

mandated screening. In particular, some metabolic researchers worried that it might preclude ever learning what proportion of infants with elevated blood phenylalanine levels were actually at risk of retardation. Nonetheless, these and other doubts about mandated testing did little to stifle popular enthusiasm for an advance that was seen to herald an extraordinarily promising new approach to the control of disease.

But if PKU were a harbinger of things to come, it meant the salvaging of individuals who would otherwise have left no progeny. Although therapy largely mooted the question of whether it was right to bring a disabled child into the world, it heightened interest in the problem of carriers. Of course PKU was not the only post-war medical advance that prompted worries about the gene pool; insulin therapy for diabetes was another frequently-cited case. But because screening and treatment for PKU appeared to be a template for a wide range of disabling conditions, it generated by far the most attention. If the new approach worked, the implication was that the incidence of many diseases would slowly but surely creep upward. Ironically, the promise of therapy having been realized, the condition that had served to exemplify what was wrong with eugenics was now invoked to illustrate why limits on reproduction were needed. But while the focus in the 1960s was on long-term consequences of treatment, a problem affecting the next generation emerged as treated phenylketonuric women began to reach reproductive age. For reasons to be discussed in the next section, it appeared that their children might be severely damaged. As the magnitude of the new problem of "maternal PKU" came to be appreciated, concern with the long-term faded. In comparison, it came to seem insignificant. As a researcher instrumental in sounding the alarm wrote: "For PKU, the dysgenic consequence of improved genetic fitness of phenylketonuric people is essentially negligible relative to the sudden and potentially severe consequences of maternal PKU"[29].

Coping with MPKU

In medicine, the solution to one problem often creates another, and PKU is no exception. Before the advent of mass screening, most women with PKU were severely retarded and

childless. But the fertility of treated women is nearly normal. When mass screening began in the 1960s, it was generally (although not universally) assumed that the highly restrictive diet had only to be maintained until gross brain development was complete, at about the age of five or six. As a result, the first cohort of treated women to became pregnant had virtually all discontinued the diet. But phenylalanine at high levels is a potent teratogen. Circulating in the maternal blood of women with PKU, it is actively transported across the placenta, concentrating in the fetus. Although only about 1 in 120 children born to women with PKU inherited the gene from both parents, and so the disease, it turned out that those born to untreated PKU mothers were also severely damaged, although initially it was uncertain what proportion of such children were affected, and exactly in what ways and to what degree.

As early as the mid-1960s, the "maternal PKU" syndrome was understood to be a potentially serious complication of treatment for PKU. A case report of three retarded but nonphenylketonuric children born to phenyketonuric women was published in 1957, and in the 1960s, reports of other similar cases appeared, as well as cases of nonphenylketonuric but retarded children born to mentally-normal women[30]. Moreover, a number of animal experiments indicated that phenylalanine easily crosses the placental barrier, that the phenylalanine concentration in the umbilical cord blood is much higher than in the blood of the mother, and that infant monkeys born to mothers given a phenylalanine-supplemented diet had low birth weights and learning impairments. An influential set of recommendations for newborn screening published by the World Health Organization in 1968 suggested that: "Since there is a high risk of retardation to the offspring of mothers with PKU, screening for PKU should be a part of early antenatal care (if screening status is unknown). Until the efficacy of a low protein diet during pregnancy is proven, termination of pregnancy should remain an option"[31]. Responding to mounting evidence of a potentially significant problem, some investigators also suggested reducing the amount of phenylalanine in the diet of pregnant phenylketonuric women. As early as 1966, the *New England Journal of*

Medicine editorialized in favor of this suggestion, noting with considerable understatement (as we will see) that the available formula was "not likely to be accepted with pleasure by patients who have grown accustomed to normal food," and urging development of a low-phenylalanine diet palatable to adults[32].

However, at the time, the suggestions were not pursued. The reasons for this are complex and go beyond the scope of this essay, but probably the most important was that the small community of PKU researchers and clinicians were focused on immediate questions, in particular: Was treatment always necessary? As noted earlier, there was no consensus as to the what proportion of individuals who received a positive Guthrie test were at risk of retardation, and a consequent concern that many were being treated unnecessarily. There were other pressing questions as well: How well did the diet actually work? How long was it necessary to maintain it? Was it adequate for normal growth and development? (In 1967, the PKU Collaborative Project was formed in an effort to answer questions about diet efficacy by treating all infants, but to varying degrees). On the other hand, treated women had not yet reached reproductive age. Maternal PKU was only a potential problem; moreover, no one then knew whether it was a large or small one.

That situation changed dramatically in the early 1980s. In 1980, Roger Lenke and Harvey Levy published the results of a large survey of treated and untreated pregnancies of women with elevated phenylalanine levels. They reported that the frequency of mental retardation among the offspring of women with untreated PKU was 92%—a rate at least as high as the risk of retardation in PKU. Moreover, the frequency of microencephaly in the children was 73%, while there were smaller but significant risks of congenital heart disease and low birth weight[33]. Both the frequency and the extent of damage were unexpected. Two years later, Henry Kirkman published projections of a "rebound" effect in phenylketonuria indicating that, in the absence of measures to address the problem of maternal PKU, all the benefits of screening could be erased after one generation; indeed, that the situation would be worse than if screening had never been instituted[34]. The combination of the Lenke and

Levy survey and Kirkman's epidemiologic projections galvanized the community of PKU researchers. But what to do?

One response was the MPKU Collaborative Project, begun in 1984 with the aim of establishing the efficacy of a restricted diet in preventing mental retardation and other abnormalities in women with elevated phenylalanine levels. But clearly measures had to be taken before the findings were in.

When the problem was initially recognized, clinicians apparently divided into essentially two groups: Those who urged women with PKU not to have biological children, and if they did become pregnant, to abort, and those who believed that a return to the phenylalanine-restricted diet would prevent damage, and who thus advised that pregnancies be planned[35]. The first approach seems to have predominated. "Currently, avoidance or termination of pregnancy in all women with elevated blood phenylalanine appears to be the usual recommendation," reported one clinician in 1973[36]. Similarly, the authors of a 1980 study wrote, "At present, females with classical and variant forms of PKU are advised not to become pregnant for fear of fetal damage" (although they themselves suggested a more nuanced approach)[37]. But even members of the second group assumed that the women they advised would maintain good metabolic control during their planned pregnancies. It does not seem that anyone thought that reproductive issues were the province of the woman alone.

The PKU diet is restrictive, unappetizing, and burdensome to prepare; emotional stress in affected families is high. Unlike most medical diets, the PKU regimen consists both of food that must be consumed and food that must be largely or wholly avoided. The prohibited or restricted foods include all proteins, including bread, pasta, rice, and other common foods—even the consumption of vegetables must be limited[38]. Synthetic substitutes are available for some items, such as bread and pasta, but among other shortcomings, they are costly and rarely reimbursed by insurance. To compensate for the lack of protein and provide calories, it is also necessary to drink a phenylalanine-free formula consisting of the other amino acids as well as vitamins and minerals. Amino acids do not taste or smell good, which is why the formula is so often described as unpalatable.

Moreover, adhering to the diet is socially awkward. Food is not only about nutrition; sharing meals is a way to build and maintain relationships. Thus strong social and cultural pressures undermine efforts to sustain metabolic control. Moreover, while dietary therapy prevents retardation, even early-treated individuals often experience some cognitive and psycho-social deficits. Thus although the current recommendation is "diet for life," most adolescents and adults are understandably not in control — even when they think they are.

Adhering to the diet during pregnancy is especially challenging. Because phenylalanine levels that are safe for the mother may damage the fetus, it is necessary to maintain very strict metabolic control during pregnancy. It is especially important in the first trimester, when the risk of fetal damage is greatest. (Since it takes time to reduce phenylalanine levels to an acceptable level, the diet should be resumed at least three months prior to conception). Pregnant women are expected to drink about 25% more of the formula, although tolerance for it is typically lower during pregnancy, especially in the first trimester. For these and other reasons, most women are not in compliance at the start of a pregnancy. A recent survey by the Centers for Disease Control found that two thirds of the women in the study were not on diet at the time they became pregnant[39]. Many will eventually achieve it, reducing the risk to the fetus. For those who do not, the risk statistics remain as grim as Lenke and Levy reported[40].

But today, unlike the situation in the early 1980s, clinicians are unlikely to admit that they tell women who are unable or unwilling to maintain good metabolic control not to have biological children. For a number of reasons, talk of reproductive responsibility has gone decidedly out of fashion, especially in the realm of genetics and in spite of an otherwise broad trend towards fetal protection, especially where a live birth is expected[41]. Since PKU is a genetic disease (even though MPKU is not), the official position is that the clinician's role is to help clients actualize their reproductive desires, whatever these may be. Counseling is expected to be non-directive. But it seems a safe bet that many clinicians who actually work in metabolic clinics believe that women with PKU should not have babies unless and

until they can manage the diet. If so, their attitude may help explain why 90% of untreated women abort their pregnancies (one important reason that the rebound in mental retardation has been much less than Kirkman's projection)[42].

However, we no longer have a language to discuss this issue openly. "All women with PKU should be strongly encouraged to receive family planning and preconceptual counseling," asserts the Committee on Genetics of the American College of Obstetricians and Gynecologists[43]. According to the recent NIH Consensus Statement (2000), there should be more "outreach and educational programs" for women of child-bearing age, which focus, among other factors, on "conscious reproductive choice." "If conception occurs when the woman is not in metabolic control, counseling should be offered"[44]. But as to what the counselor is supposed to say, the recommendations are silent[45].. It is understandable that authors would evade rather than confront the issue, but a trend toward avoiding discussion or driving it underground may not be a particularly healthy development.

Acknowledgments

Diane Paul's work on the history of newborn screening has been supported by the National Science Foundation under grant No. SBR-9511909. She is indebted to Harvey Levy for insights into the history of maternal PKU, especially in the 1970s and '80s; to Chris Jolly for his efficient work tracking down Linus Pauling's Ford Foundation grant proposal and related correspondence in the Ava Helen and Linus Pauling Papers at Oregon State University; to the archivists in Special Collections at Oregon State for permission to cite from these materials; to Bruno Strasser for his willingness to share materials; and to members of the PKU Planning Group at Children's Hospital, Boston, whose monthly meetings continue to be a source of both insights and inspiration.

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