

## CHAPTER 7

### The Struggle Over Metabolic Screening

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The ailment is rare, but its importance is not to be measured in terms of numbers alone ... The study of PKU promises to help uncover the causes of other hereditary disorders, particularly the basis for other types of mental deficiency. The disorder thus exemplifies many so-called molecular diseases, and the rewards that may accrue from the ceaseless probing of these points on the far frontiers of modern bio-medical research. (Harold M. Schmeck Jr. *The New York Times*, 1961, p. 8).

#### INTRODUCTION

Newborn screening for phenylketonuria (PKU) is today among the most routine of medical procedures. In many countries, including the U.S., Canada, the nations of Western and most of Eastern Europe, Israel, Egypt, Japan, Australia and New Zealand, virtually all infants are tested for this autosomal recessive disease. Unless the parents receive a positive result, they may not be aware that a test has been done, even in those American states where they have the legal right of refusal.

The incidence of PKU in the U.S. is estimated at about one in every 10,000 births. When mass screening began in the early 1960s, it was thought to be even lower; about one in 25,000. A 1939 survey by the American physician George Jervis found that 0.79% of patients in fourteen institutions for the mentally retarded were diagnosed with PKU (Jervis, 1939). A 1962 Children's Bureau census identified 399 children with PKU who had been admitted to programs for the mentally retarded during the preceding five years, on average 80 cases per year.

How and why did such a relatively rare condition become the focus of so much attention? The answer might seem to be obvious. Most untreated individuals with PKU are profoundly retarded and suffer from other physical and behavioral

abnormalities; some are unable to walk or talk or control their bowels or bladder. In the 1950s, a number of studies indicated that restricting infants' dietary intake of phenylalanine could prevent or mitigate retardation and other symptoms associated with PKU in the same way that galactosemia, an even rarer metabolic disorder, might be treated by substituting a soy bean-based substitute for milk. (Medical genetics texts of the 1950s often accorded galactosemia more attention than PKU).

These studies led some hospitals to test infants for PKU. The diagnosis was made on wet diapers using a strip of filter paper that immediately turned green when a drop of ferric chloride solution was added. But as this urine screening test was unreliable until the age of six to eight weeks, after the infant had been discharged from the hospital and possibly after he or she had already suffered some degree of irreversible brain damage, it did not work well enough for purposes of early identification of affected infants.

In 1960, a new test was developed, which was more sensitive than the urine test and could be administered while the infant was still in the hospital. In its initial form, the heel of the newborn was pricked and the resulting blood dried on discs of filter paper. The paper was placed on the surface of an agar culture plate containing an analogue of phenylalanine,  $\beta$ -2-thienylalanine, and spores of *Bacillus subtilis*. While normally these bacteria are capable of synthesizing their own phenylalanine, the presence of  $\beta$ -2-thienylalanine blocks a crucial metabolic step in this process and the bacteria cannot reproduce. When a filter paper disc impregnated with blood from an affected individual is placed on the medium, however, the high levels of phenylalanine which it contains diffuse into the medium, and are available to the bacteria to overcome their phenylalanine starvation, producing a zone of growth surrounding the disc.

Two years after this test became available, Massachusetts became the first state to mandate PKU screening. By 1965, 32 states had enacted screening laws, all but five making the test mandatory; by 1975, virtually all newborns in the U.S. were being tested. In some states the laws passed with neither hearings nor floor debates and by acclamation or voice vote without dissent.

Before the new test had been validated or the effects of dietary treatment assessed, the PKU program was being cited as a model for the screening and prevention of other metabolic disorders. Thus at a March of Dimes symposium in 1967, the detection of PKU was characterized as "a model system for the application of genetic screening to public health" (Honeyman and Gabrielson, 1968, p. 100). Although a five-year collaborative study of treated phenylketonuric children for purposes of evaluating dietary therapy only began in 1967, Katherine Oettinger, then Chief of the U.S. Children's Bureau, characterized PKU screening in a December 14, 1965 press release as "a breakthrough in the prevention of mental retardation," noting that it "has paved the way for similar screening procedures for other inborn metabolic errors." Before the decade had ended, a variety of other rare metabolic conditions were being detected with the same filter paper blood specimen employed for PKU screening (Guthrie, 1968; 1992).

Newborn screening for PKU is often characterized as a triumph of applied human genetics and as the program that linked genetics to public health (see Paul, in press). Even in the 1960s, it was claimed that PKU, "because it can be both detected and prevented, has opened the public health door to genetics and genetic screening" (Honeyman and Gabrielson, 1968, p. 100), although neither the test nor treatment for PKU was (or is) genetic. Charles Scriver reflects the common perspective that every test of an inherited disorder involves genetics when he writes that, by 1970, "newborn screening for PKU had become one of the most widely applied genetic technologies in human society" (Scriver, 1994). But PKU screening was not a genetic technology as that term is generally understood today. Guthrie's test was employed to identify affected newborns, not parent carriers from whom the disease might in future be inherited.

In the 1930s, Lionel Penrose suggested that PKU heterozygotes were more prone to senile dementia, leading some scientists to hope that the condition could be detected early and carriers prevented or discouraged from mating with each other (Haldane, 1941, p. 139; see also Munro, 1947). Carrier detection finally became a reality in 1956, when the geneticist David Yi-Yung Hsia and colleagues at Harvard Medical School found that clinically asymptomatic heterozygotes could be identified through the use of a phenylalanine tolerance test. (With half the normal enzyme activity, carriers are unable to efficiently metabolize the additional load of phenylalanine, which can be detected in the blood). The use of that technology would indeed have constituted genetic testing in the stricter sense. But while some geneticists expressed hope that carrier detection plus counseling might represent "an important method of control" of the disease, that prospect was never realized (Honeyman and Gabrielson, 1968, p. 103; see also Hsia, 1968, pp. 83-84; Sutton, 1961, p. 93). The loading test was not very reliable and attracted little interest among high-risk individuals or their physicians.

Newborn screening, on the other hand, was quickly routinized. This may appear a logical result of the invention of a reliable and cost-effective test combined with the discovery that exclusion of dietary phenylalanine prevents retardation in PKU. That is indeed the standard account. But at the time mass screening was adopted, neither the reliability of the test nor the efficacy of the PKU diet had been proven. Researchers in the field of human metabolism argued that the legislated screening was premature and that some infants might even be harmed by the diet. They protested that not enough was known about the disease, the test, or the proposed treatment to justify large-scale legislated screening programs. Moreover, there was no effective therapy — then or now — for some of the other "inborn errors of metabolism" (or as they were increasingly called, "molecular diseases") that were soon piggy-backed onto the system for PKU testing. To its critics, these programs represented a vast and uncontrolled experiment being perpetrated on a naive and unsuspecting public.

Thus the road to mandatory screening, while short, was far from smooth. From a distance, its introduction in the 1960s may appear the inevitable result of

advances in diagnosis and therapy. But a closer examination shows that there was no inexorable bridge from the science to the screening programs. Screening was the product of a well-crafted political campaign pursued in the context of a more general shift from social toward biological approaches to mental retardation. Given its low incidence, PKU did not directly touch many lives. But the political constituency for PKU screening was much larger than the number of affected individuals and their families might suggest. That constituency quickly overwhelmed the opposition from researchers (and also from physicians concerned about malpractice suits). In this chapter, we explain how scientific and political trends intersected to produce enthusiasm for a molecular approach to the problem of mental retardation.

### THE SCIENTIFIC BACKGROUND TO SCREENING

Phenylketonuria was first described in 1934 by the Norwegian physician and biochemist Ivar Asbjørn Følling, who recognized the condition as one of Archibald Garrod's "inborn errors of metabolism." When Følling added ferric chloride to the urine of two severely retarded children (then a standard procedure to detect ketones in the urine of diabetics), a deep green color developed. The substance responsible was found to be an abnormal metabolite, phenylpyruvic acid. To learn if other mentally-retarded patients also excreted this acid, Følling collected samples from 430 patients and demonstrated the green color in eight. He hypothesized that phenylpyruvic acid was produced when patients were unable to metabolize phenylalanine normally (Følling, 1994, pp. 5-6). In 1939, George Jervis confirmed that an excess of phenylalanine was associated with the condition Følling called "oligophrenia phenylpyruvica" and identified the cause as an inability to convert phenylalanine to tyrosine (Jervis, 1939; Jervis *et al.*, 1940). He also demonstrated that this inability results from a defect in the liver enzyme phenylalanine hydroxylase (Jervis, 1953).

Among Følling's original ten patients were three pairs of siblings, suggesting a genetic basis for the condition. In 1935, a pedigree analysis suggested to Penrose that the disease (which he and biochemist Juda Quastel renamed phenylketonuria) was probably inherited in a recessive manner. Penrose's hypothesis was soon confirmed by Jervis, who analyzed 213 institutionalized patients and concluded that the condition was due to a single autosomal recessive gene (Jervis 1939). Jervis and his colleague Richard Block also proposed that affected babies be fed a diet from which the phenylalanine had been removed through a filtering process (Laurence, 1939; Jervis and Block, 1939). At the time, their proposal did not arouse interest among specialists in mental retardation, who apparently thought it far-fetched (Brecher and Brecher 1959, p. 109). In Britain, Penrose had also experimented with low-phenylalanine diets in the 1930s. But he was discouraged from pursuing the experiment by Frederick Gowland Hopkins (then Britain's leading biochemist) on the grounds

that it would cost 1000 pounds sterling per week to feed one patient on the synthetic phenylalanine-free diet (Kevles 1985, pp. 177-178).

However, in 1951 the idea of dietary therapy was revived by the English biochemists Louis I. Woolf and David G. Vulliamy at the Hospital for Sick Children in London. They suggested that high levels of phenylalanine or one of its intermediary metabolites circulating in the blood was responsible for the symptoms of PKU and suggested that, "if the amount of phenylalanine and the breakdown products could be reduced, normal cerebral function might result" (Woolf and Vulliamy, 1951, p. 151). Using charcoal to extract the unwanted phenylalanine from their foods, Woolf tested the theory on three small children; all showed some improvement. In the early 1950s, groups associated with Horst Bickel (1954) at the Children's Hospital in Birmingham, England, with Marvin Armstrong and Frank Tyler (1955) at the University of Utah College of Medicine, and with Frederick Horner and Charles Streamer (1956) at the University of Colorado Medical School also reported cognitive and behavioral improvement of children treated with a low-phenylalanine diet. Although some other groups were less successful, and the first retrospective statistical study confirming the benefit of dietary therapy only appeared in 1960 (Knox, 1960), the positive reports generated great excitement.

That enthusiasm is easy to understand. The field of mental retardation was then considered "the ultimate in therapeutic hopelessness" (Cooke, 1964, p. 392). Lamenting physician disinterest in the field, one neurologist conceded that it was in part "a reflection of the undeniable fact that, in the majority of instances of mental retardation, medical treatment has little to offer" (Masland, Sarason, and Gladwin, 1958, p. 26). Now it seemed that an understanding of biochemistry might actually lead to a cure — and not just for PKU. Even in the 1950s, when treatment (mostly with young children) had only begun and preliminary results were mixed, dietary therapy in PKU was already being cited as a successful model for other metabolic disorders.

### POLITICAL BACKGROUND TO SCREENING

During the late 1950s, both private and governmental organizations in the U.S. began to rethink their traditional emphasis on the social approach to retardation. Of particular importance in this reorientation was the role of the parents' group, the National Association for Retarded Children (NARC). Organized in 1950, the NARC had been very effective in lobbying Congress and the Children's Bureau of the Department of Health, Education, and Welfare (HEW) to expand their support of programs for the mentally retarded (Edelson, 1994, pp. 7-8).

The NARC's initial interest was largely in expansion of educational, social, and rehabilitative services. That emphasis coincided with the approach favored at HEW, where it was thought that many parents of the retarded "would be happy to take care of their children in their own homes, if necessary supporting

services were available to them in their own communities." But Representative John Fogarty, chair of the subcommittee on health of the House Appropriations Committee, thought the money would be best used in a search for biological, and especially hereditary, causes of mental illness (Edelson, 1994, pp. 4-5).

At the same time, the NARC's own position was shifting. In the mid-1950s, it commissioned a survey of the field in connection with a program aimed at discovering causes of and ways of preventing mental retardation. Two reports, one on prevention and the other on psychological and cultural factors in mental subnormality, were published in 1958. The author of the report on prevention was Richard Masland, a young neurologist and neuroscientist, and a member of the NARC's Scientific Advisory Board. He suggested: "the time is ripe for a large-scale attack on the genetically determined defects" through the application of new techniques to the study of basic metabolism and to the study of patients suffering from mental deficiency (Masland *et al.*, 1958, p. 50).

These developments converged with the election of John F. Kennedy as U.S. President. The President's sister Rosemary had long been institutionalized for mental retardation and the subject was one of great personal interest to the entire Kennedy family. In 1961, President Kennedy announced a major new initiative in this area. He stressed that five million Americans were mentally retarded — a number far larger than the number of persons suffering from diabetes, polio, and other diseases which were the focus of intense public concern and the targets of major government expenditures. Moreover, facilities for the care of mentally retarded persons were vastly overburdened. State institutions averaged 367 patients above their rated capacities while for the 160,000 patients in public institutions, there were only 500 full-time physicians. Thus there existed a huge imbalance between the scope of the problem of mental retardation and the efforts to address it. On current educational and rehabilitative approaches, "the central problem remains unsolved, for the causes and treatment of mental retardation are largely untouched" (Kennedy, 1962, p. 496). The President promised to seek to double the amount spent by the National Institutes of Health in this field. He also announced the appointment of a Presidential Advisory Commission on Mental Retardation headed by Leonard Mayo, Executive Director of the Association for the Aid of Crippled Children. The panel was charged with appraising the adequacy of existing programs and recommending future action.

The Commission's appointees included Elizabeth Boggs, the NARC's Research Chairman and proponent of the scientific approach to retardation, and its proposals strongly reflected the NARC's perspective. Thus the panel's staff urged the Advertising Council to circulate information about the PKU field trials in states without legislated screening, a proposal that even Children's Bureau officials doubted was appropriate (Theodore D. Tjossem to Arthur J. Lesser, July 9, 1964). When the Commission's recommendations were published, they included a statement that newborn screening and the management of metabolic disorders was an "important" step in preventing mental retardation, and recommended that such programs be expanded although at this time the only U.S.

experience with newborn screening programs involved the unreliable ferric chloride urine test, which missed many cases. Thus the attractiveness of such approaches lay not in their specific accomplishments, but rather in the hopefulness generated by the idea that science could be mobilized to rescue America from the large and apparently intractable problem of mental retardation (Edelson, 1994). As yet, hope was nearly all that science could offer.

At just this time, Robert Guthrie, a microbiologist and non-practicing physician, developed a cheap, sensitive, and simple bacterial inhibition test. Guthrie had a retarded son and a niece who had been diagnosed with PKU at 15 months, too late to benefit from therapy. This personal interest in the disease led him to devise an assay for monitoring the blood phenylalanine level of children on low-phenylalanine diets. It soon became clear that the same test could be used to measure blood phenylalanine levels in newborns, with the possibility of beginning dietary therapy before irreversible brain damage had occurred. It was also found that the blood or serum sample did not need to be fresh, making it possible to process samples in batches at central laboratories to which test samples could be regularly mailed (Guthrie, 1973, pp. 229-30; 1992, pp. 6-7).

Soon after inventing the test, Guthrie proposed both to the Children's Bureau and to Elizabeth Boggs of the NARC that it be field tested for suitability in a national screening program for all newborns. The Children's Bureau agreed. In late 1961, it commenced a field trial involving over 400,000 infants in 29 states. A number of researchers expressed concern that the Bureau was already committed to a screening program based on the Guthrie test — a charge indignantly denied by Bureau staff. A regional medical director protested: "So far as I know, no member of the Bureau staff questions the need for further testing of the method. At this point it is not intended as a recommended screening program" (Lucille J. Marsh to Franklin D. Yoder, June 4, 1962). But by the time the trial ended in 1963, the Bureau had aggressively taken up the screening cause. While it was forbidden by statute from promoting state legislation, its slogan became "Test Every Newborn for PKU."

## RESPONSE TO THE GUTHRIE TEST

Announcement of the Guthrie test was greeted in a number of quarters with elation. Even before the field trial had ended, and in spite of the rarity of the disease, it was hailed as a major discovery. The American Medical Association included the Guthrie test in its 1962 year-end report on several major medical breakthroughs, along with the cracking of the genetic code (*New York Times*, 1963; Wehrwein, 1963). PKU was now discussed everywhere — in newspapers and magazines ranging from *Good Housekeeping*, *Better Homes and Gardens*, and *Life*, to *Today's Health*, *Scientific American*, and the *Saturday Review*. The significance accorded the disease is reflected in the first awards for outstanding achievement presented by the Joseph P. Kennedy, Jr. Foundation in 1962: the

recipients were Joe Hin Tijo, Jerome Lejeune, Murray Barr — and Følling. The Advertising Council campaign featured ads with the heading: "A fifty cent test spared this baby from spending his life mentally retarded." The following text appeared to the right of a picture of an obviously normal infant (Figure 7.1):

## A fifty cent test spared this baby from spending his life mentally retarded.



But only in Massachusetts, New York, Louisiana and Rhode Island is the test legally required.

There is a disorder of body chemistry called phenylketonuria, or PKU. Once, there was no way to diagnose it. Once, babies born with it were doomed to lifelong mental retardation.

But no longer. For a new test — given during the first few days of life — detects PKU before brain damage occurs. A special diet corrects the trouble. A PKU baby then grows and develops as normally as any other child.

The test costs only 50c a baby. But a PKU victim, undiscovered, can cost \$100,000 for lifetime care in an institution.

If your state doesn't require the PKU test, urge its adoption. It should be a must for all babies everywhere.

1. If you expect a baby, urge a doctor's test of phenylalanine levels in the baby's urine to diagnose it. Once, babies born with it were doomed to lifelong mental retardation.
2. If you have a baby, urge a doctor's test of phenylalanine levels in the baby's urine to diagnose it. Once, babies born with it were doomed to lifelong mental retardation.
3. Urge your state to require the PKU test for all babies.
4. Urge your state to require the PKU test for all babies.
5. Urge your state to require the PKU test for all babies.
6. Urge your state to require the PKU test for all babies.
7. Urge your state to require the PKU test for all babies.
8. Urge your state to require the PKU test for all babies.
9. Urge your state to require the PKU test for all babies.
10. Urge your state to require the PKU test for all babies.

Please return enclosed post card to the Advertising Council, 22 West 41st Street, New York 18, N. Y.

But only in Massachusetts, New York, Louisiana and Rhode Island is the test legally required.

There is a disorder of body chemistry called phenylketonuria, or PKU. Once, there was no way to diagnose it. Once, babies born with it were doomed to lifelong mental retardation.

But no longer. For a new test — given during the first few days of life — detects PKU before brain damage occurs. A special diet corrects the trouble. A PKU baby then grows and develops as normally as any other child.

The test costs only 50c a baby. But a PKU victim, undiscovered, can cost \$100,000 for lifetime care in an institution.

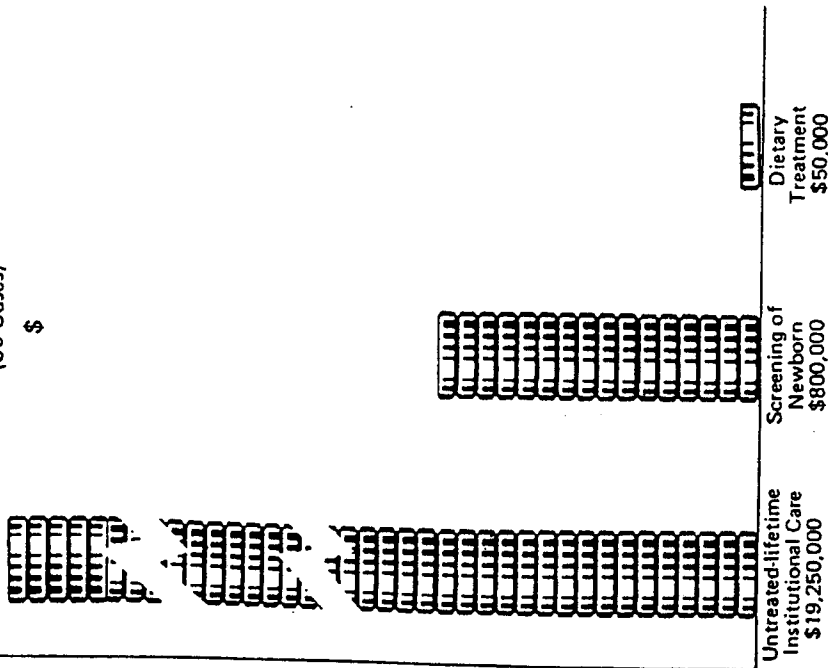
If your state doesn't require the PKU test, urge its adoption. It should be a must for all babies everywhere.

Screening advocates regularly emphasized the cost effectiveness of the program when lobbying the federal or state legislatures. Arthur Lesser, Director of the Children's Bureau Division of Health Services, testified to a subcommittee of the House Committee on Appropriations in 1961 that PKU testing had saved the federal government \$2 million. Some cost-benefit claims simply compared the cost of a single test to the cost of lifetime institutionalized care. More sophisticated analyses compared the expense of laboratory testing and evaluation and treatment for metabolic disorders with the assumed expenses to the state of institutionalized care (typically for twenty years) for a proportion of the affected infants and the costs of medical and hospital care for the non-institutionalized. On this basis, Massachusetts officials estimated a saving of \$364,662 per year (Massachusetts Department of Public Health, 1974). The expense of laboratory testing was sometimes equated with the unit cost of the test rather than the cost of identifying one affected individual — perhaps because the latter would include the cost of retesting the large number of false positives intrinsic to screening for very rare conditions. (In the early years of screening, the false positive rate was 95 percent; that is, there were nineteen false positives for every true one). And the costs of treatment were equated with the expense of providing the special dietary formula rather than the panoply of medical and social services usually required for effective therapy (Figure 7.2).

In some cases, reporters and politicians vastly overstated the significance of PKU as a cause of mental retardation. Thus Senator Joseph Montoya asserted: "The Department of Health, Education, and Welfare has reported that there are approximately 5.5 million mentally retarded in the United States today. Many of those are a result of phenylketonuria and mental retardation and could have been

Figure 7.1. Advertising Council campaign for PKU testing.

**COST OF PKU (Phenylketonuria)  
(50 Cases)**



**Figure 7.2.** Cost of life-time institutional care of PKU patients, compared with cost of screening newborns and of dietary treatment.

prevented if detected in infancy. Most of the state training schools for the mentally retarded are overcrowded and have long waiting lists for admission” (Congressional Record, 27919, Oct. 21, 1965; see also Brecher and Brecher, 1959, p. 32).

However, most commentators understood that PKU was a rare disease, whose prevention would not begin to solve the problem of overcrowding in institutions for the mentally retarded. They viewed the Guthrie test as a major medical breakthrough because they considered PKU a model for the prevention of other diseases. If it could be prevented, why not the other inborn errors of metabolism? Indeed, why not mental disorders of other types? Thus after noting that fewer than 500 individuals with phenylketonuria are born each year, one author wrote:

But the relatively low incidence of PKU is no measure of the attention it is currently receiving, especially from mental health experts. Their interest is easily explained: Never before has mental retardation been proved to have a known organic cause. The discovery of such a cause in the case of PKU has exciting implications. It suggests that, in time, certain other mental ailments including schizophrenia and manic-depressive psychosis — may be found to have similar roots. And, naturally, the discovery of organic origins for a disease tends to hasten its cure and prevention (Greer, 1966, p. 25).

Commentators often implied that cures were just around the corner or even already at hand. Referring to galactosemia, cystic fibrosis of the pancreas, glycogen storage disease, and idiopathic hyperlipemia, one author wrote: “These diseases can now be readily diagnosed and controlled by changes in diet” (Pompian, 1961, p. 61). According to a January 14, 1963 report in *Newsweek*: “With their new knowledge about the chemical processes underlying heredity, scientists are rapidly approaching the control of such disorders as PKU, not just by diet, but altering the faulty gene itself” (p. 70).

These discussions reflect the success of biochemist Linus Pauling’s project to view diseases — including mental diseases — in molecular terms. By the 1960s, PKU was often referred to as a “molecular disease,” a term coined by Pauling in 1949 to characterize sickle-cell anemia, a condition whose molecular basis he had described (Pauling, 1949; see also Kay, 1993; and de Chadarevian, this volume). The term soon gained a wide currency and broad meaning; by the 1960s it was often employed synonymously with “inborn error of metabolism” (Fraser, 1961, p. 59; Penrose, 1967, p. 18).

While not all commentary was positive, the few skeptical voices were heard only after screening was already near-universal (e.g. *New York Times*, May 4, 1968, p. 1). Many researchers would have preferred a more cautious approach to screening but they were also very cautious in their criticism. They did not complain to the press or legislators. In general, they kept their doubts to themselves. The Committee on Nutrition of the American Academy of Pediatrics criticized many aspects of the metabolic screening programs in a July 30, 1965 report to the Children’s Bureau. Its members argued that:

- (1) The objectives and ways and means for implementing such wide scale screening programs remain to be evaluated as do the methods for following through of patients with heritable metabolic diseases detected by such programs.
- (2) The beneficial effects of good dietary management of any of the heritable metabolic diseases ... have yet to be proven unequivocally. Under the circumstances, the committee felt that caution was indicated in launching widespread screening programs until practical therapeutic programs, the effects of which are predictable in the majority of children participating, have been designed.

(3) It must be demonstrated with certainty that any normal children who receive these restrictive diets through inadvertence or because of misdiagnosis will not suffer irreparable neurological or physical damage.

But the committee declined to publish its full report.

Samuel P. Bessman, a University of Maryland pediatrician and biochemist, was an exception to the rule that skeptical researchers did not take their case to the public. With political scientist Joseph Cooper, he lobbied tirelessly in opposition to legislated screening. Bessman and Cooper testified before state and federal legislative committees, gave speeches, wrote letters to the editor. Bessman also testified for the defense in a highly publicized malpractice suit, arguing that both the nature of the disease process and the efficacy of dietary therapy were open to question. He suggested that the improvement shown by children on the diet might be explained by the extra attention they received from parents, doctors, and other therapists (e.g. Bessman, 1966). A once highly respected PKU researcher, he is now something of a pariah in the field. But the association of Bessman with opposition to mass screening has obscured the fact that less confrontational colleagues shared many of his concerns. Thus in their summary of the proceedings of a 1966 Children's Bureau-supported conference on PKU, the editors criticized "legislation which has included public pressure for a specific therapy at a time when competent medical investigators are not in agreement on the criteria for diagnosis, natural course of the disease or optimal therapy or therapies" (Anderson and Swaiman, 1967, p. 238; see also Berry and Wright, 1967).

### SOURCES OF SKEPTICISM

It was initially intended that the results of Guthrie blood testing would be compared with later more definitive blood or urine tests. In fact, little systematic comparison was ever carried out. Thus there was no direct comparison of this method with other screening tests at that time, no effort to define its reliability in the face of other compounds that might be present in newborn blood samples, no assessment of the test's reliability when administered very early in life, before the infant had been fed a sufficient protein load, and no agreement on what level of blood phenylalanine was optimal. Consequently, there was no clear "gold standard" for the diagnosis of PKU that would allow an accurate estimate of its sensitivity and specificity — characteristics crucial to determining the actual value the test would have. Moreover, in most cases, initial screening positives were confirmed by a second Guthrie test, with the test allowed to be its own criterion for accuracy (Edelson, 1994, p. 11). No detailed evaluation of testing was published in a peer-reviewed journal — a sensitive point with PKU researchers. (That Guthrie was an outsider to the human metabolic research community, who took his case directly to parents, press, and government, did not help his relations with scientists).

Moreover, newborn blood testing uncovered many more apparent cases of PKU than would have been predicted on the basis of studies of the mentally

retarded. It was soon evident that elevated blood phenylalanine levels could result from conditions other than "classical" PKU. But it was unclear what proportion of these individuals were actually at risk of retardation.

Particularly worrisome was the prospect that some infants were being harmed through too-drastic treatment. Phenylalanine is an essential dietary amino acid, not synthesized by humans but necessary for survival and growth. Too little as well as too much may be harmful. Louis Woolf himself believed that as many as half of all newborn phenylketonurics might not require treatment, although he considered the financial costs and rigors and the dangers of unnecessary therapy "a small price to pay for preventing the mental deterioration otherwise inevitable" in those affected (Woolf, 1967, p. 58). While some researchers asserted that little harm would come from treating non-PKU infants, others worried that it could produce mental retardation. (For a range of views, see Anderson and Swaiman, 1967, pp. 59–61, 113–115). Problems in dietary management were compounded by uncertainty about the true phenylalanine content of foods and the unpalatability of the low-phenylalanine formula. In the first years of screening, some infants suffered severe malnutrition either as the result of too severe restriction of phenylalanine or of diet refusal (Kang, December 21, 1965).

Moreover, proponents of screening often asserted that only infants and young children required treatment. When gross brain development was complete — around the age of five — they thought it would be possible to resume a normal diet. But the skeptics maintained that no one knew if this were in fact true. A committee of the American Academy of Pediatrics noted: "Because an adequate and reliable diet first became available in this country in late 1958 and because early screening tests have only recently come into general use, only a few patients have been discovered within the first month of life. Even they have been treated for less than six years, and this period of time is inadequate for assessing child development and projecting eventual intellectual ability on optimum treatment" (Committee on the Handicapped Child, 1965, p. 502).

Some researchers also noted that intensive social and psychological support services would be required if dietary therapy were to be effective. Even after counseling, most parents understood little about the disease, and many could not cope adequately with the diet (Sibinga and Friedman, 1971). Skeptics predicted that these problems would only mount if it turned out that the restrictive and unpalatable diet had to be maintained beyond early childhood.

A few researchers were dubious that the abnormalities associated with PKU resulted from an excess of phenylalanine. Theirs was a minority view. But no one did understand why extra phenylalanine should be harmful or knew whether the damage was produced by the amino acid or one of its intermediary metabolites.

Bessman in particular argued that these and other scientific questions would be difficult or even impossible to answer once screening and treatment were universal. He protested that, "if all children with excess of some amino acid in their blood are placed on deprivation therapy, we shall never know the natural history

of any new disease or what the actual risk of mental retardation may be" and pleaded for controlled clinical trials (Bessman, 1966, p. 337).

The lack of placebo-controlled trials disturbed members of the Children's Bureau technical advisory committee as well. They argued that experiments should be designed to show whether there was value in therapy for tyrosinemia "before medico-legal problems, which have arisen in PKU, prevent an objective and scientific evaluation of the treatment of this metabolic disease also" (Children's Bureau, March 11, 1966). Even a Children's Bureau official noted that she had become much more conservative as the result of defending the agency's stance regarding PKU and other metabolic disorders. "The implications of 'widespread distribution' of prematurely drawn conclusions have been criticized — and rightfully in my estimation," she wrote. "We have a responsibility not only to be 'purveyors of information relating to child health and welfare' but also to use judgment in what we 'purvey' and to foresee the results of such activity" (Kang, 1967). That view was echoed by the members of the Committee on the Handicapped Child, who complained that "exaggerated predictions for normal development regardless of the age of discovery and irrespective of the strictness of the diet or of the hereditary endowment have led to frustration and discouragement on the part of pediatricians and parents" (1965, p. 503).

## CONCLUSION

Researchers in human metabolism were concerned that too little was known about the diagnosis and treatment of PKU to justify mandated screening. But while their concerns were wide-ranging, they were almost invariably technical. Only Joseph Cooper, the social scientist, asked whether screening programs would divert resources from more pressing needs of the mentally retarded.

We must face the question: Would the same resources which are now put into rare conditions yield greater benefits if they were devoted to more pressing or more prevalent matters? ... less than 1% of the retarded population in hospitals consists of PKU-diagnosed patients. What of the other 99%? Other problems of more widespread significance ... are in need of social and legislative action. What are we doing, for example, about the home-situated retardees who awaken one day to find that their parents or relatives are gone or no longer able to care for them? What do we do about these people? They must certainly outnumber those with PKU (Cooper 1965, pp. 12-13).

Responding to Cooper's claim that undue emphasis given to PKU would result in a slighting of the needs of the vast majority of institutionalized retardates, Robert Guthrie charged that Cooper "missed the point that those of us who have been excited about PKU realize that PKU is a 'model' ... for future accomplishment with many of the other inborn errors of metabolism" and went on to note that "the specific prevention of mental retardation in PKU has had a marked

effect in increasing the interest of medical investigators and practitioners in the general problem of mental retardation" (February 7, 1966). But Guthrie also missed Cooper's point that science could not solve the problem of individuals who needed social support in order to live outside an institution. Indeed, mass testing was followed by a turning-away from the service-oriented approach originally favored by both the Children's Bureau and the NARC. In the 1950s, their emphasis had been on putting services in place to permit children to stay in their homes. Screening programs promoted the attitude that the problem of childhood mental retardation was now in some sense "solved." Only with the emergence of de-institutionalization in the 1970s were movements for community-based services for the retarded revived.

But arguments that pit the interests of possible future beneficiaries against the interests of those with a clear and direct and immediate stake in the outcome are rarely effective. One constituency is already mobilized; the other is simply conjected. Arguments about the need for controlled clinical trials seem equally abstract to legislators and the public. As in contemporary research on treatment for AIDS or high-dose chemotherapy for breast cancer, such arguments failed to persuade those whose interests were most immediate and who were thus most politically engaged. As David Hsia commented to a reporter, while he was personally unsure of the value of mass screening, "Yet the parents of such [PKU] children realize its worth" (Lyons, 1968). Then as now, the view that scientific explanations — especially in terms of molecules — can provide the solution to refractory social problems exerted a powerful appeal. Despite this appeal, the molecularization of treatment was vigorously contested. The issues that troubled the early history of metabolic screening continue to be among the thorniest and most intractable in contemporary biomedicine and society.

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## CHAPTER 8

### "A 'Cage' of Ovulating Females": The History of the Early Oral Contraceptive Pill Clinical Trials, 1950-1959

Lara Marks

In 1955 Katherine McCormick, the chief financier of the early development of the oral contraceptive pill, complained bitterly about the difficulties the investigators were experiencing in recruiting the right type of women to participate in trials. The real problem, as she put it, was how to get a "cage" of ovulating females to experiment with.<sup>1</sup> What is most striking is McCormick's suggestion that women could be reduced to their reproductive physiology, i.e. that they could be seen merely as "ovulating females". Indeed, the notion that women could be reduced to their reproductive physiology was the very foundation on which the early trials of the pill were built. Reproductive physiology itself was also conceived merely as an interplay between various hormonal molecules which could be manipulated within the body by introducing new chemical hormones (Oudshoorn, 1994). In this sense, the pill was part and parcel of the molecularization of reproduction.

McCormick's words indicate, however, that this approach faced obstacles. It could be argued that in alluding to a "cage" of "ovulating females", McCormick believed that women could be treated merely as animals. Nonetheless, those undertaking the early clinical trials of the pill soon discovered that the practical application of a reductionist perspective of reproductive physiology was much more difficult in the case of the trials with women than with animals. As this chapter highlights, women, unlike animals, were free agents in their own right and could not be monitored 24 hours every day. McCormick herself admitted,

Human females are not easy to investigate as are rabbits in cages. The latter can be intensively *controlled all the time*, whereas the human females leave town at