Phenylketonuria in New York State

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THE REPORTING and registering of persons having phenylketonuria (PKU) in New York State is required by the public health law (*1*). Prior to the mandatory screening of newborn infants for phenylketonuria by New York and many other States, epidemiologic data were based on surveys or on selected populations. Frequency of phenylketonuria in the State, for example, could only be estimated from an institutional census (*2*) or from a report of blood phenylalanine levels in residents of the State schools for the mentally retarded, according to G. A. Jervis, State department of mental hygiene, in personal communications to the authors. In our report the incidence in New York State of phenylketonuria at birth is estimated and is related to its prevalence in the total population.

Method

The incidence of phenylketonuria at birth in 1965 and 1966 was estimated from reports to the director of the State's bureau of maternal and child health of confirmed cases of PKU in infants with hyperphenylalaninemia. The infants were referred from a statewide screening to clinicians in four State-supported PKU treatment centers. The referrals were made when the infant's initial sample contained greater than 20 mg. of phenylalanine per 100 ml. of blood or when a second sample contained 6 mg. or more. Initial samples were taken on the day of hospital discharge and were assayed by a microbiological inhibition method (*3*, *4*). Second samples were taken, usually within the first 3 weeks of life, and if the initial concentration were 4 mg. or more, the samples were assayed by spectrofluorometric method (*5*).

The criteria for confirming phenylketonuria varied with the clinician; in 30 of 31 patients for whom the information was available, however, the hyperphenylalaninemia was 20 mg. or more before treatment and urine samples contained abnormal metabolites. A diagnosis of tyrosinemia of prematurity was excluded, since the hyperphenylalaninemia and urinary metabolites increased with age (up to the time of treatment), and the serum tyrosine, when included in the clinicians' reports, was not elevated. Serum levels in one patient were no greater than 15 mg. and the patient had normal urine; both parents of the patient, however, were identified as carriers when tested by the loading dose response.

An estimate of the prevalence of phenylketonuria in the total population was made by enumerating the known patients from the following sources: infants detected in the screening of blood at birth previously mentioned; residents and outpatients known to have PKU in the 19 hospitals for the mentally ill, seven schools

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for mental defectives, and a school for epileptics of the State department of mental hygiene; persons with phenylketonuria known to the four outpatient facilities later designated by the bureau of maternal and child health as PKU treatment centers prior to, or as relatives of patients identified in, the mandatory screening program at birth; persons with phenylketonuria known to physicians in private practice; and siblings and close relatives who were located in visits to homes of patients.

The number of live births were those registered with the New York State Department of Health in 1965 and 1966; the total population of New York State in December 1966 was estimated arithmetically from 1950 and 1960 Federal census figures. The number of resident mental retardates was obtained from the New York State Department of Mental Hygiene.

Results

Twenty-two newborn infants were reported as having phenylketonuria in 1965, and 24 were reported in 1966. There were 336,605 live births in 1965, and 322,662 in 1966, giving an incidence rate of phenylketonuria at birth (to the nearest 1,000) of one in 15,000 in 1965, and one in 13,000 in 1966. Approximately half the infants identified in the statewide screening and about 40 percent of all the persons with phenylketonuria were from the New York City area.

In a total population of 17,953,570 in the State, 418 persons had phenylketonuria, which gives a point prevalence of phenylketonuria in New York of one in 43,000 in December 1966. Eleven percent were infants identified in the screening program since January 1965. The distribution of the persons having phenylketonuria in December 1966 was as follows:

Source	*Number*
State institutions:	
Residents	219
Outpatients	88
Treatment centers (excludes those screened at birth)	57
Tested for PKU at birth (January 1965–December 1966)	46
Physicians in private practice	2
Home visits	6
Total	418

The ascertainment of phenylketonuria in the two population groups differed in method. The infants were identified through the biochemical parameters of the disease in blood and urine; most persons with phenylketonuria in the general population (exclusive of infants screened at birth) were identified after clinical signs of the condition appeared.

Ascertainment of phenylketonuria in infants was more complete than in the general population. Incidence at birth was estimated from testing 97 percent of the population in 1965, and 99 percent in 1966 of the total live infants born. These percentages did not include infants lost so early in the neonatal period that they were not tested nor infants not born in a hospital or not brought for PKU testing to a hospital (less than 1 percent). Prevalence was estimated from a selected segment of the total population, that is, individual persons and families who came to medical attention.

Coverage within the selected segments of the total population varied in completeness. Three-fourths of the persons having phenylketonuria were located in a group of 25,000 mentally retarded residents of, outpatients at, or transfers from State schools. Students at six of the State schools for mental retardates and the school for epileptics had been screened for phenylketonuria by blood test within a few years of our enumeration. Not screened and not included in our survey (1965–66) were retardates in non-State institutions, persons subsequently admitted to the six State schools, or those in special classes for the retarded in public schools, day care centers for the retarded, vocational services with a significant caseload of retarded (including sheltered workshops) and other outpatient facilities. Five persons with phenylketonuria were located in one State hospital; none of its patients, to our knowledge, had been screened.

Fourteen percent of the persons having phenylketonuria were known to clinicians in treatment centers prior to or as relatives of patients diagnosed as having phenylketonuria by the mandatory blood screening. The survey for known phenylketonurics among physicians in private practice was not comprehensive.

Six siblings with hyperphenylalaninemia of greater than 15 mg., exclusive of those already mentioned, were located among 300 relatives in visits to 30 families of a person known to have phenylketonuria. Our yield of presumably affected siblings per index-case family visited,

one for every five families, agrees with the Centerwalls' experience in California (*6*) and suggests a cluster of 60 persons or more having phenylketonuria yet to be located among the families of persons known to have PKU not visited at the time of our enumeration.

Discussion

The apparent threefold discrepancy in incidence and prevalence of PKU observed here may have several origins as suggested earlier (*7*). Incidence was estimated in a reference population of infants; prevalence, in one of persons of all ages, including infants. The degrees of being populations-at-risk varied. Of the infants, 97 and 99 percent were a population-at-risk for the event enumerated in 1965 and 1966, that is, biochemical (and potential) PKU. Few persons in the general population were a population-at-risk for the same event in December 1966, that is, those who had symptoms suggesting PKU so that a diagnosis of biochemical PKU was sought.

Different stages of the disease were ascertained in the two reference populations: biochemical (potential) phenylketonuria in the infants and clinical (oligophrenic) phenylketonuria in the total population. The relationship between the different stages of the disease, assumed usually to be direct and one of development, is controversial (*7*) and, because of present prophylactic schedules, may never be defined.

Other clues to a less-than-direct relationship lie in the occasional reports of phenylketonuria with minimal or no oligophrenia (*8a*, *9–11*). These reports leave little doubt that the biochemical defect occurs unrecognized in the general population; other persons possibly having phenylketonuria are those with convulsive disorders or persistent eczema. The elusive parent of phenocopy phenylketonuria (*8b*, *12*) also escapes identification and has yet to be systematically sought for during the prenatal period or in mothers of persons with mental retardation of undefined cause (*13*).

The following two factors are applicable in any estimation of prevalence rates. A presumed higher death rate among persons having phenylketonuria, as adjudged by the greater skew of their age distribution and lower median age than those of other institutionalized retardates (*2*), may have reduced the average duration of the disease. Nonspecific mortality rates for the appropriate age groups in the total population have contributed to the discrepancy also, since the two reference populations differed in age.

These differences in incidence and prevalence rates will affect estimates of the gene frequency. If the homozygote is identified by the biochemical parameters only, and by incidence at birth, one in 15,000, the gene frequency will be one in 123, and the carrier rate, one in 62. If the homozygote frequency is chosen as the prevalence rate of the oligophrenic form, one in 43,000, the gene frequency will be one in 200, and the carrier rate, one in 100.

The various forms of hyperphenylalaninemia found in the screening at birth and their outcome are an issue for a later discussion and serve here as the initial clue to phenylketonuria. No comparison was made with prevalence rates reported earlier (*14*, *15*), or with incidence rates from other recent large-scale screening programs (*16*).

Summary

An incidence rate of phenylketonuria in newborn infants in New York State was estimated as one in 15,000 in 1965 and one in 13,000 in 1966, from data acquired in a statewide mandatory screening of blood phenylalanine. The prevalence of the clinical form of the disease in the total population in December 1966 was estimated as one in 43,000 from data assembled in a canvass of State schools of mental retardates, State mental hospitals, or by examination of relatives of persons known to have phenylketonuria. Within the limits of the prevalence estimate, the discrepancy suggests a reservoir of unrecognized hyperphenylalaninemia in the community.

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Hearing Loss in U.S. Population

An estimated 4 million persons in the United States have some hearing loss in both ears. An additional 2.5 million (13.5 persons per 1,000 population) are estimated to have loss of hearing in one ear.

These data from the National Center for Health Statistics of the Public Health Service were obtained for the year ending June 1963 from a nationwide sampling of household interviews. Forty-two thousand households, comprising about 134,000 persons, were visited.

Impaired hearing was defined on the basis of the severity of hearing loss, using responses to a series of scaled questions related to the ability to hear and understand speech without a hearing aid.

Of the 22.3 persons per 1,000 population with hearing loss in both ears, 4.7 were unable to hear and understand spoken words, an additional 4 persons could hear and understand only a few spoken words and 13.3 persons could hear and understand most spoken words. The remaining 0.3 percent could not be classified as to their hearing impairment.

Loss of hearing in both ears increased steadily with age, from 3.5 persons per 1,000 population under 17 years to 132 persons per 1,000 who were 65 years and older. Men suffered more hearing loss in both ears than women, with 25.5 men per 1,000 population in contrast to 19.1 women per 1,000. The prevalence of hearing loss in both ears decreased as family income and education increased.

The prevalence of impaired hearing in both ears was found to be lowest in urban areas. For persons 65 years and older, the rates were highest among rural, nonfarm residents. In each age group, the rates were lowest in the northeastern area of the nation and highest in the South and West.

White persons had a higher rate of impaired hearing in both ears than nonwhite persons, with 23.3 whites per 1,000 in contrast to 15.1 nonwhites per 1,000 population.

Hearing aids were used at the time of the interviews by about 22 percent of the population with impaired hearing, according to the study. More women (24.5 percent) than men (19.2 percent) used hearing aids.