This progress report of the experience of the State Health Department in using the Guthrie Test for phenylketonuria on all babies born in Massachusetts is of considerable interest. In the first place, it is an ambitious undertaking successfully carried out, secondly it may stimulate others, and thirdly it is an indication of a broader approach to inborn errors of metabolism.

NEWBORN PHENYLKETONURIA DETECTION PROGRAM IN MASSACHUSETTS

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THE Diagnostic Laboratories of the Massachusetts Department of Public Health and the Division of Maternal and Child Health were happy to join in the general phenylketonuria (PKU) detection program sponsored by the Children's Bureau. It was initiated in the summer of 1962, using the bacterial inhibition screening procedure devised by Dr. Robert Guthrie of the Children's Hospital in Buffalo, N. Y.[1] Rather than test only the quota of 10,000 newborns assigned to Massachusetts, it was decided in the beginning to set as a goal the testing of all the babies born yearly in the Commonwealth, estimated at 112,000. All the maternity hospitals were therefore invited on a voluntary basis to enter the program.

Actually it was quite logical for the state to embark on a full-scale program. The Division of Maternal and Child Health was already encouraging well child conferences to test for PKU, and had been furnishing the services of a district nutritionist to assist the families of known cases. Concern stemmed from reports of these field workers about serious hardships facing low income families caring for several afflicted children. In 1962, support was given by legislation enabling the Department of Public Health to inaugurate a program to combat mental retardation in children suffering from this genetic defect. The Children's Bureau therefore approved utilization of federal Fund A to initiate the state-wide screening of all newborns.

In getting ready to launch the program, we brought together at a large meeting hospital administrators, health department personnel who would be responsible for providing the state services, and physicians heading pediatric, obstetrical, laboratory, and nursing services. It was explained that the hospitals would assume responsibility for the collection of the filter paper heel blood on the day of the baby's discharge from the hospital. These samples would be mailed weekly to the Diagnostic Laboratories for processing. In addition the hospitals would give the mother the kit for the filter paper urine specimen to be obtained from the baby at three weeks of age. In this procedure the filter paper is left beneath the diaper

until wet, after which it is removed, allowed to dry, and mailed in. It was further explained to all concerned that financial aid in the treatment of phenylketonurics would be available where needed. The great importance of the program was, of course, stressed at this meeting, and repeated during an extensive educational program for professional personnel and the lay public. The continuing interest and judicious help of the Massachusetts Association and the National Association for Retarded Children were invaluable in publicity and in the educational program.

The Diagnostic Laboratories and Maternal and Child Health Divisions shared responsibility for following up the original conference by meeting with interested groups in their individual hospital settings. Although there were a number of problems to be resolved, all 115 maternity hospitals in the Commonwealth came gradually into the state program. The Health Department's Maternity Nurse Consultant was extremely helpful in instructing the hospital nurses wherever the latter assumed responsibility for explaining the test to parents, drawing the heel blood, and recording the required data. She worked effectively in the over-all educational program, which included all day sessions on PKU held throughout the state. About 1,200 public health, hospital, and visiting nurses attended these sessions. Among other matters, these meetings emphasized the necessity for obtaining from each baby three full drops of heel blood, each of which completely soaks through the filter paper, because an inadequate sample could mean a missed case. As the screening program progressed and elevated phenylalanine levels were detected, the Maternity Nurse Consultant gave priority consideration to problem cases where there was delay in following through with the recommended confirmatory test. In every instance physicians and parents cooperated, enabling a diagnosis of phenylketonuria to be established in the first weeks of life.

Table 1, which is entitled "Massachusetts Phenylketonuria Screen Testing Using Bacterial Inhibition Assay" shows the statistical growth for the first year and a half of the program in Massachusetts. The first column, headed "Newborn Bloods," shows the rather rapid increase from the beginning in mid-July, 1962, through the first six and a half months of the program. Note the asterisks appearing after the August, October, November, December, and January totals, indicating seven positive specimens during this period. Each of these was confirmed by a serum phenylalanine determination on a later specimen performed at an independent hospital. This unexpectedly high number of seven phenylketonuria cases occurring in 26,955 bloods (see cumulative total for January, 1963, in the next column), undoubtedly aided greatly in persuading the nonparticipating hospitals to enter the program rather rapidly. The staffs of the hospitals in the program as well as those not yet in the program were promptly informed of these unexpectedly early findings, including the fact that the very first case would have been missed had the particular hospital involved entered the program one week later. We were gratified to have enrolled by midwinter—well before passage of the law making PKU testing of newborns mandatory in Massachusetts—all 115 maternity hospitals in the state, including the military hospitals with obstetrical services. The program has continued with considerable favor from the hospitals and little objection.

The positive results have been gratifying, too. At the close of January, 1964, the total score is 14 detected cases in close to 135,000 newborns tested.* Each of the 14 cases has been confirmed by a serum phenylalanine test performed at

* By November 1, 1964, 27 cases in 217,752 newsborns tested.

an independent hospital, in several of the cases by paper chromatography as well.

The third column tabulates the filter paper urine specimens received. Note that in May, 1963, statistics for follow-up "4 wk bloods" begin to appear in the fourth column. Our results during the early months emphasized to us how much more reliable the filter paper bloods are than the filter paper urines. The filter paper urine tests have two major disadvantages: first, fecal contamination often gives elevated readings due to substances in the feces rather than in the urine; second, phenylalanine or its metabolites may not appear in the urine in sufficient amounts until a later date. We therefore started recommending to the mother that a filter paper blood collected through the doctor's office at the baby's four to six weeks visit would be preferable to the filter paper urine. We have been pleased to note that an increasing number of the mothers and doctors have responded to this suggestion.*

The last two columns indicate the total follow-ups obtained. The "+ ?" symbols are added to point out that in addition to the known follow-up specimens there is an unknown additional number of follow-up tests done in the doctors' offices by the ferric chloride or Phenistix

* Beginning November 1, 1964, all follow-ups are to be filter paper bloods.

Table 1—Massachusetts Phenylketonuria Screen Testing Using Bacterial Inhibition Assay

	Newborn Bloods	Cumulative Totals	Follow-up Urines	Follow-up "4 wk Bloods"	Total Follow-ups	Total Follow-ups as Per cent of Newborn Bloods
July 16-31, 1962	269	269	42		42	
August, 1962	1,601*	1,870	579		579	
September, 1962	2,040	3,910	1,304		1,304	
October, 1962	3,789**	7,699	2,267		2,267	
November, 1962	5,492*	13,191	4,130		4,130	
December, 1962	5,626*	18,817	3,636		3,636	
January, 1963	8,138**	26,955	6,229		6,229	77%
February, 1963	7,544	34,499	5,050		5,050	67%
March, 1963	8,237*	42,736	5,729		5,729	70%
April, 1963	9,680*	52,416	6,126		6,126	63%
May, 1963	8,703	61,119	4,960	1,372	5,332+?	61%+?
June, 1963	9,284	70,403	3,496	2,059	5,555+?	60%+?
July, 1963	10,091	80,494	3,275	2,437	5,712+?	57%+?
August, 1963	9,233*	89,727	2,648	2,918	5,566+?	60%+?
September, 1963	8,866	98,593	1,953	3,254	5,207+?	59%+?
October, 1963	10,298*	108,891	2,911	3,982*	6,893+?	67%+?
November, 1963	8,048	116,939	2,127	4,061	6,188+?	77%+?
December, 1963	8,873*	125,812	2,141	4,261	6,402+?	72%+?
January, 1964	8,768*	134,580	2,466	5,060	7,526+?	86%+?

* Each asterisk represents the inclusion of a positive specimen confirmed by a serum phenylalanine determination on a later specimen.

NOTE: An average of about 1 in 2,000 newborn bloods has shown a moderately increased reading of 6 to 12 mg % (normal 1 to 4 mg %) which has necessitated repeat studies on later specimens; one of these, which on a later specimen had a reading over 20 mg %, proved to be phenylketonuric. In all, three bloods over 20 mg % by the screening test were not confirmed as phenylketonurics; two of these were from prematures.

Table 2

PKU Baby and Birth Date	Results of Guthrie Bacterial Inhibition Tests	Confirmatory Phenylalanine Serum Levels
No. 1 (girl) 8/15/62	8/21/62 blood over 20 mg % 9/7/62 blood over 20 mg %	8/30/62 serum 54.5 mg % (LaDu method) 9/7/62 serum 60.7 mg % Both done at Children's Hospital, Boston
	Her follow-up urine was negative with the ferric chloride test, and 6-8 mg % using the bacterial inhibition test. (This baby later died of a pneumonia, apparently unrelated to the PKU condition.)	
No. 2 (girl) 10/6/62	10/12/62 blood over 20 mg % 10/17/62 blood over 20 mg %	10/17/62 serum 54.2 mg % (LaDu method) St. Vincent's Hospital, Worcester
	No urine specimen was submitted.	
No. 3 (boy) 10/14/62	10/18/62 blood over 20 mg % 10/24/62 blood over 20 mg %	10/31/62 serum 36.4 mg % (LaDu) Children's Hospital, Boston
	His urine was positive 11/1 by ferric chloride test.	
No. 4 (girl) 11/5/62	11/9/62 blood over 20 mg % 11/16/62 blood over 20 mg %	11/23/62 serum 64 mg % (LaDu) Children's Hospital, Boston
	No urine specimen was submitted.	
No. 5 (girl) 12/17/62	12/22/62 blood over 20 mg %	1/7/63 serum 47.5 mg % (LaDu) Children's Hospital, Boston 1/7/63 serum 59.8 mg % (LaDu) St. Vincent's Hospital, Worcester 1/7/63 serum over 40 mg % Children's Hospital, Buffalo
	No urine specimen was submitted. (Later, baby reported died in crib with suffocation; autopsy declined.)	
No. 6 (boy) 1/10/63 (No. 6 and No. 7 are two of triplet brothers 4-6 wks premature)	1/25/63 blood over 20 mg % 1/31/63 blood over 20 mg % 2/9/63 blood over 20 mg %	1/31/63 serum 54.5 mg % (LaDu) Children's Hospital, Boston
	His urine on 1/24 was above 12 mg %, and on 2/9 above 20 mg % both by bacterial inhibition test.	
No. 7 (boy) (No. 6 and No. 7 are two of triplet brothers 4-6 wks premature)	1/25/63 blood over 20 mg % 1/31/63 blood over 20 mg % 2/9/63 blood over 20 mg %	1/31/63 serum 49.0 mg % (LaDu) Children's Hospital, Boston
	His urine on 1/24 was above 12 mg %, and on 2/9 normal both by bacterial inhibition test. (3rd triplet brother all normal levels.)	
No. 8 (boy) 2/27/63	3/5/63 blood over 20 mg % 3/18/63 blood over 20 mg %	3/18/63 serum 36.0 mg % (LaDu) Children's Hospital, Boston
	His follow-up urine was positive with the ferric chloride test.	

Babies No. 2, No. 5, No. 6, No. 7, and No. 10 through No. 14 confirmed also by paper chromatography.

Table 2—(Continued)

PKU Baby and Birth Date	Results of Guthrie Bacterial Inhibition Tests	Confirmatory Phenylalanine Serum Levels
No. 9 (girl) 4/12/63	4/14/63 blood 6 to 8 mg % 4/30/63 blood over 20 mg %	5/4/63 serum 24.2 mg % St. Vincent's Hospital, Worcester
	Her urine (4/29/63) was negative by bacterial inhibition and Phenistix tests.	
No. 10 (boy) 7/16/63 about six wks premature	8/6/63 blood over 20 mg % 8/7/63 blood over 20 mg %	8/9/63 serum 41 mg % (LaDu) Children's Hospital, Boston
	His urine was positive by Phenistix test and about 12 mg % by bacterial inhibition test. Loading tests of both parents consistent for PKU carriers. (Of 3 older sisters, 2 are normal by Guthrie blood test and urine Phenistix. The third child, however, who was 17 months old, had bacterial inhibition blood test over 20 mg % and urine Phenistix strongly positive. Also, mother has 2 PKU cousins—one deceased and one on treatment.)	
No. 11 (boy) 10/3/63	10/11/63 blood over 20 mg % 10/21/63 blood over 20 mg % 10/19/63 urine over 20 mg %	10/22/63 serum 66.8 mg % (LaDu) Children's Hospital, Boston
	His follow-up urine was positive with the ferric chloride test.	
No. 12 (boy) 9/18/63	10/17/63 blood over 20 mg % 10/19/63 blood over 20 mg %	10/22/63 serum 29.2 mg % (LaDu) Children's Hospital, Boston
	His follow-up urine was negative with ferric chloride test as performed by the baby's doctor. This case was detected from the follow-up sample of blood taken at 4 weeks of age. The first sample, taken at the hospital when the child had been feeding for two days, had readings one disc between 4 and 6 mg % and one disc 4 mg % at the Diagnostic Laboratories. A subsequent test done on a parallel sample was performed at the Children's Hospital, Buffalo, N. Y. which gave a reading of 4 mg %. A repeat blood sample was not requested because the phenylalanine elevations were not at the 6 mg % level which this laboratory used then as the basis for requesting repeat specimens. This particular specimen was one of a group which had been autoclaved for one hour (dry heat) in order to prepare them for paper chromatography; however, so were the controls which were used for comparison.	
No. 13 (girl) 12/12/63	12/17/63 blood over 20 mg % 12/28/63 serum over 50 mg %	12/28/63 serum 53.4 mg % (LaDu) Children's Hospital, Boston
No. 14 (boy) 1/7/64	1/11/64 blood 12 mg % 1/24/64 blood 20 mg %	1/29/64 serum 23.2 mg % (LaDu)
	His urine (1/24/64) was negative by bacterial inhibition assay.	

Babies No. 2, No. 5, No. 6, No. 7, and No. 10 through No. 14 confirmed also by paper chromatography.

methods. We are nevertheless concerned about the follow-up tests that are not done.

It should be noted that there is an asterisk after the October, 1963, "4 wk bloods," indicating that a phenylketonuric infant not discovered through the original newborn blood test was detected through the "4 week blood" test. This event graphically illustrates not only the need for the follow-up specimens, but also the desirability for a greater follow-up re-

sponse. We now individually request the baby's physician to secure a follow-up filter paper blood specimen on each newborn baby whose blood exhibits a 4 mg per cent or higher level.*

The important details of the 14 phenylketonuria cases detected are given in tabular form in Table 2. Note that in most cases the initial reading of the blood test was over 20 mg per cent (normal 1 to 4 mg per cent). Case No. 9, however, discharged from the hospital at two days of age exhibited a level of 6-8 mg per cent, which on a second specimen at 18 days of age was over 20 mg per cent. Case No. 12 is the child first detected through the "4 wks blood" test. Case No. 10 is a premature baby in whom we further substantiated the diagnosis by phenylalanine loading tests of the parents. In the routine check of the siblings of this baby, a 17-month-old sister also was discovered as a previously unsuspected phenylketonuric.

The Guthrie bacterial inhibition test, we find, performs quite satisfactorily. It is not technically difficult, although we advise that professionally trained workers should be in charge. In our hands, the results of the test have agreed closely with serum phenylalanine determinations when the latter have been done. About one in 2,000 newborn bloods has shown a moderately increased reading of 6 to 12 mg per cent, necessitating repeat studies on later specimens; a later specimen from one of these newborns as we have noted above, exhibited a reading of over 20 mg per cent and the baby was confirmed as a phenylketonuric. The others proved not to be phenylketonurics; they are examples, instead, of the moderate transient elevations which occur from time to time in normal babies, and more frequently in premature babies.[2] In all, three bloods over 20 mg per cent by the screening test were not confirmed as phenylketonurics; two of these were from prematures. Moderately increased levels which are transient should not be termed false-positives, since they do correctly indicate an actual increased level of phenylalanine. They are not particularly troublesome even though they do indicate the need for the study of later specimens.

Along with the importance of detecting phenylketonurics especially in the newborns, goes also the importance of having facilities for intelligent treatment of the cases discovered. While therapy is quite satisfactory if skillfully administered, rather meticulous management is required. Phenylalanine is an essential amino acid, and fatal outcomes have been reported in the literature when the level has been allowed to drop too low. In the Massachusetts Program, as soon as a diagnosis is definite notification is sent to Services for Crippled Children as well as to the baby's doctor. The doctor is informed that the department supports a clinic for children with phenylketonuria and other inborn errors of metabolism. This clinic is available at no charge for consultation services or complete medical services. At the present time about 50 patients are enrolled in the clinic including older children and the babies detected in the screening program.

The cost of the program has not been excessive. The investment of about 30,000 dollars during the first year of the program, less than 50 cents per child tested, has led to the discovery

* In such a case the mother also is tested for phenylketonuria. If positive, dietary treatment should be considered during later pregnancies to prevent possible brain damage to the fetus in utero. Equally important, when the newborn PKU girls we are discovering and getting under the prompt dietary treatment finally grow up to have babies of their own, they must be alerted—perhaps as the responsibility of a permanent, working PKU registry—that plans regarding resumption of dietary treatment during pregnancy will have to be worked out. This should be by the obstetrician in consultation with the pediatric expert, for skillful adjustment is needed so that the fetus in utero will not be damaged either by too high or too low a phenylalanine level in the mother's blood.

of ten new phenylketonuric babies before the development of irreversible brain damage. The total cost for the year has been perhaps half the cost of maintaining one of these children in an institution for life. The disorder—now appearing to occur about once in 10,000 births—is definitely considerably more frequent than the earlier estimates. Certainly the project has proved most rewarding, and the screening program ought to expand widely. In our state, joint planning between the two divisions will continue and will, we hope, soon be extended to provide for similar early detection and control of other inborn errors of metabolism, such as galactosemia and maple syrup urine disease. We are already trying out on a pilot basis new screening tests devised by Guthrie for these disorders.[3]

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800 Per cent Increase in Lung Cancer Deaths

Lung cancer has had the greatest rise—more than 800 per cent—in mortality of any noninfectious disease in the United States over the last 30 years. The cause is generally attributed to the increase in cigarette smoking. At the same time, the American Cancer Society points out, deaths from stomach cancer have shown a sharp, dramatic drop. The cause is unknown.

U. S. Navy Medical News Letter 44:24 (Oct.), 1964.