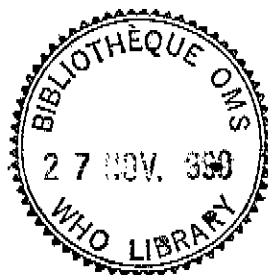


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GUIDELINES ON THE PREVENTION AND CONTROL OF PHENYLKETONURIA (PKU)



DIVISION OF NONCOMMUNICABLE DISEASES
AND HEALTH TECHNOLOGY

HEREDITARY DISEASES PROGRAMME

1990

I. General Principles for Formulation of National Screening Programmes
for Phenylketonuria in Developing Countries

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1. INTRODUCTION

In 1934, Folling¹ reported phenylketonuria (PKU) as an inherited metabolic disorder associated with mental retardation. In subsequent years, urine testing through paper chromatography and other chemical procedures allowed initiation of preliminary screening techniques. In 1953, Bickel's² report of the effectiveness of treatment in reducing at least some of the clinical brain damage resulting from PKU suggested that early detection coupled with appropriate therapy might prevent mental retardation in these patients. Guthrie's³ methodology for bacterial testing for phenylalanine and other metabolites on blood specimens dried onto filter paper opened the door to a sensitive efficient laboratory procedure for screening newborn infants for PKU.

Since the early 1960's, newborn screening programmes for various disorders have evolved based on Guthrie's simple methodology and the ease of specimen transport when blood is collected onto filter paper. Although early comparative studies of the Guthrie PKU procedure showed mixed results with respect to reliability, subsequent experiences removed any doubts as to the usefulness of bacterial inhibition assays (BIA). Fluorometric procedures have also been utilized in conjunction with both serum and filter paper specimens. The methodology of McCaman and Robins⁴ has been most widely favoured for fluorometric serum analysis while the modification of this procedure by Hill et al⁵, made analysis from filter paper specimens a suitable alternative. The later methodology has been further modified by Hoffman et al⁶, to allow for simultaneous testing for galactosemia. Enzymatic assays for phenylalanine, on the other hand, have not yet become practical for large-scale screening.

Either the bacterial or the fluorometric procedure is suitable for large-scale screening of infants and many examples of successful programmes utilizing either methodology exist. It is well documented that both techniques are suitable for use with large numbers of specimens, are sensitive and specific to the analyte of interest, may be run on specimens transported long distances and are economical. Additionally, collection of the appropriate filter paper specimen causes minimal inconveniences to medical personnel, parents, and the infants screened. Once collected, this filter paper newborn specimen is potentially available for other testing.

This report is intended to provide guidance and resource material for those developing nations who are considering the organization of a neonatal screening programme for PKU. It is hoped that the outline provided here will prevent unnecessary difficulties already overcome in other developed programmes which might slow progress in programme implementation. Over the past few years, screeners from around the world have formulated a network of professionals who have profited from the experiences of other members of the group and developing programmes should take advantage of these contacts.

2. SITUATION ANALYSIS

Phenylketonuria is an autosomal recessive disorder. It is estimated that one person in 60 is a heterozygous carrier of the mutant. The worldwide incidence of PKU is approximately 1 in 12,000-15,000 births. The incidence varies widely from country to country and even within countries. For instance, the incidence in Ireland has been reported as 1:4500⁷ while the incidence in the Netherlands is approximately 1:26,000⁸. Incidence variations also occur among ethnic groups within the same geographic area. PKU has been only rarely reported among American blacks and in Israel seems to be limited to groups other than Ashkenazic Jews⁹. While ethnic composition is probably the most predominant influence on the incidence of PKU, statistical considerations must be looked at carefully due to differences in definitions of PKU and other forms of hyperphenylalaninemia.

Phenylalanine, while essential for human growth and development and present in all natural foods containing protein, may accumulate in the blood and urine when an individual is lacking in the liver enzyme phenylalanine hydroxylase. Deficiency of this enzyme blocks the catalysis of phenylalanine and its metabolites. It is this excess of phenylalanine or one of its metabolites which is thought to inhibit the biochemical processes needed for normal brain development. Deficiency of tyrosine caused by the inability to metabolize phenylalanine leads to inhibition of melanin development causing a decrease in pigment formation. Thus, light hair, light eyes and fair skin are observed in many PKU patients. An equally characteristic musty odor in PKU patients results from excretion of excess phenylacetic acid into the urine and sweat.

Early screening tests relied on Folling's observation that excessive phenylpyruvic acid in urine results in a green colour change in the presence of ferric chloride. This "wet diaper" testing and its analogs have long since been replaced by bacterial and fluorescent testing. Neonatal urine testing is not considered accurate, and therefore is undesirable for screening, since not all PKU infants have phenylpyruvic acid in their urine in the first days of life. Similarly, certain drugs and other disorders can also lead to false positive results with the urine test.

Recent fact sheets published by the American Academy of Pediatrics (AAP)¹⁰ note that screening tests are usually from dried blood spots on filter paper taken from heel sticks and blood phenylalanine levels are measured by bacterial inhibition or fluorescent assays or in some cases by aminoacid analysis. The sensitivity of testing is dependent upon the level of phenylalanine used as a cut-off value and the age and protein intake of the patient at the time of testing. This report notes that infants tested prior to 24 hours of age and utilizing a 4 mg/dL cut-off will result in missing 16% of cases while screening at 24-48 hours of age will result in missing only 2.2% of cases. The testing specificity of these screening methods is noted to be 99.9%. Optimal screening should occur in infants older than 24 hours and before 7 days of age. While some have advised that rescreening should be performed on all infants at 1-4 weeks, the AAP fact sheets note that such follow-up testing may not be cost effective. Further AAP emphasis is also given to the need for testing all infants before 7 days of age regardless of prematurity, illness, feeding history or antibiotic treatment.

Classical PKU is not considered to be a life ending disorder. Nonetheless, studies of institutionalized patients have shown a definite reduction in life span. On the other hand, cofactor variants may lead to childhood deaths.

Reduced intelligence may be expected in 95% of untreated or late diagnosed PKU. Common clinical symptomatology involves convulsions, hyperactivity and eczema, however, clinical diagnoses are rarely made before 6 months of age and usually only after there are obvious signs of mental retardation.

In most current public health settings worldwide, screening and diagnosis of PKU lead to treatment through low phenylalanine dietary management. Where commercial dietary products exist, public funds are often utilized for financial support of such management. Economic situations, however, may dictate private funding of these dietary products (either partially or wholly) and in some instances where commercial products are unavailable, medical research products may be utilized for patient nutrition. When proper dietary management is initiated before 4 weeks of age, such intervention has been highly effective in reducing mental impairment in patients with classical PKU. Cofactor related causes of hyperphenylalaninemia, on the other hand, may require other treatment and the outcome may be less desirable. Phenylalanine levels below 10-15 ug/dL in patients considered to be hyperphenylalaninemic may require no treatment.

Therapy is best coordinated by a physician in conjunction with a trained metabolic nutritionist. Periodic laboratory monitoring of phenylalanine levels is helpful in maintaining the appropriate amounts of low phenylalanine diet, protein foods. Artificial sweeteners containing aspartame are considered hazardous. Treatment of adults, especially women of childbearing age, is generally recommended and, while treatment after central nervous system damage will not reverse the damage, some improvement in behaviour control may be realized. Current research efforts have provided prenatal diagnosis and carrier testing through DNA analysis. The efficacy of treatment for prevention of fetal effects is being studied and preliminary data suggest that treatment begun prior to conception and continuing throughout the pregnancy may be beneficial.

The Committee on Genetics of the AAP has addressed the components of an idealized screening programme for the persistent hyperphenylalaninemias (PHP), including PKU, and for congenital hypothyroidism in a set of recommendations. While admittedly aimed at improving a "developed" system, these guidelines should serve as goals in those "developing" areas of the world beginning neonatal screening for PKU. "An adequate screening programme for PHP ... should assure:

- (a) Total participation by the eligible population.
- (b) Notification of parents about newborn screening and their participation in this activity.
- (c) Reliable and prompt performance of the screening test.
- (d) Prompt follow-up of subjects with positive tests.
- (e) Accurate diagnosis of subjects with confirmed positive tests.
- (f) Appropriate counselling and treatment of patients".

These guidelines further define an adequate blood specimen as "heel" blood obtained as close as possible to the time of discharge from the nursery in healthy full term infants and at or near the seventh day of life in all others. Infants screened before 24 hours of age are at higher risk for missed diagnosis

through laboratory testing and follow-up testing should be considered. The analytical component of the programme is best standardized through centralization of the laboratory.

In order to implement a national screening programme for PKU, a great deal of planning must occur and a number of hurdles must be overcome. It is essential that a programme not be undertaken without a mechanism to produce the desired outcome. It must be fully understood that newborn screening comprises several components which must function together as a unit in order to produce the desired results. Initially it is important to gather information allowing the programme organizer to:

- (a) Assess the expected incidence of PKU within the population.
- (b) Determine the availability of, and mechanism for securing the dietary products necessary for treatment of the PKU.
- (c) Calculate the economic impact of case detection including cost savings from not having to provide specialized care for these detected cases.
- (d) Review procedures and identify facilities for laboratory analysis of specimens.
- (e) Review specimen collection and transport problems relative to the local situation.
- (f) Identify individuals who are proponents of screening in order to form a nucleus of expert advisers with technical expertise and political savvy.
- (g) Determine revenue resources which might be tapped in order to support the screening programme.
- (h) Develop a schedule for implementing each aspect of a comprehensive programme.
- (i) Prepare written delineation of responsibility for each of the professional roles in the programme.
- (j) Develop a case registry to monitor patient outcome.
- (k) Develop a plan to assist older females with disease management during childbearing years.
- (l) Determine the statistical tabulations of interest for programme monitoring and develop a mechanism for their capture.

In planning the overall screening system it is essential that at least four elements of screening be addressed:

- (a) Health care provider.
- (b) Laboratory.
- (c) Follow-up system.

(d) Treatment mechanism.

Each of these programme components must be carefully developed. A detailed description of the operation, function, and degree of involvement (including beginning and ending points) of each must be clearly thought out and written down. This operational guide must be realistic in its expectations and not so idealistic as to be nonfunctional.

Health care provider (HCP)

Health care providers must be educated as to the importance of a properly collected and timed specimen. A written procedure for specimen collection, specimen transport and record keeping should be provided to all potential specimen submitters (physicians, mid-wives, etc.). A suggested protocol for specimen collection from premature and/or sick infants should be developed along with retest guidelines for patients having elevated or moderately elevated phenylalanine levels. Guidelines for appropriate actions in testing for nonclassical variants should also be provided. The responsibility of the HCP in collecting a specimen suitable for analysis cannot be overemphasized. Training of collection personnel should be considered through educational literature, audio-visual aids, and/or personal contact.

Laboratory

A centralized laboratory capable of analyzing at least 30,000 to 50,000 specimens should be considered. Larger capacities are acceptable, however, laboratories analyzing fewer specimens have traditionally exhibited a greater percentage of "missed" cases. Inaccuracies in the laboratory result from a lack of proficiency in detecting extremely rare disorders, therefore, effective quality control is essential. Reliable standards properly used are mandatory as are use of both external and internal quality assurance materials. Blinded proficiency testing of the laboratory's abilities at detection are highly desirable. A clearly written laboratory procedure manual should exist which documents not only the technical protocol but also the responsibilities of the laboratory in determining specimen suitability and reporting results (both to HCP and follow-up personnel).

Follow-up system

A system must exist whereby a responsible party receives laboratory results, performs follow-up testing (if necessary) and initiates, or refers patient for treatment. A statistically determined cut-off value should be used for triggering follow-up serum testing such that test sensitivity allows a small number of "false positives" with a minimal number of the "false negatives". Most screening programmes today use a value of 4 mg/dL for this value. Some programmes retest filter paper specimens when the initial value is considered "low abnormal", choosing to run serum analyses only on those with significantly elevated screening values (>10 mg/dL). Many, however, perform serum retests of all patients exhibiting screening values >4 mg/dL as a means of decreasing time to treatment of all potential cases. Clear written guidelines must delineate the follow-up person's responsibilities including contact protocols and documentation methodologies as well as the beginning and ending point of the follow-up procedure. In most cases, follow-up begins with transmittal of abnormal results from the laboratory and ends with documentation of patient treatment (including annual status reports). It should be the responsibility of the follow-up system to assure the patient access to dietary supplementation.

Treatment mechanism

Treatment has been most effective when accomplished through both medical and nutritional combined efforts. Periodic visits to a knowledgeable physician coupled with dietary support from a trained nutritionist provide the patient and his family with the needed resources to accomplish the desired outcome. Parental education is paramount in assuring dietary compliance. A parental support group should be organized wherever possible. If it is not appropriate for dietary products to be supplied to the patient by the screening programme, other mechanisms should be sought for financial assistance to the patient so that dietary compliance can be assured. Periodic evaluations of blood phenylalanine are most effective in measuring control of the disorder and a mechanism for this testing should be available.

Comparative review

Policy and programme comparisons with other states or countries are often useful in defending and promoting screening programme design. Certain items which might be useful for this comparison are listed below:

- State or national legislation - is there a law requiring neonatal screening and is it structured so that PKU is included? Do rules and regulations governing screening exist?
- Screening responsibility - is the responsibility for obtaining a specimen clearly defined?
- Specimen - is a satisfactory specimen defined with respect to both quantity and timing?
- Transport - does a system exist to transport the specimen to the laboratory in a timely manner?
- Laboratory - is there a centralized laboratory performing high volume analyses?
- Follow-up - does a formal follow-up system exist which assures accomplishment of the screening goals?
- Treatment - is the dietary supplement readily available and what is the mechanism by which it may be secured by the patient? Is professional treatment/management available?
- Quality control - is there an established mechanism for assuring quality control of the screening programme throughout?
- Advisory committee - does an advisory committee exist and what is its makeup and function?
- Expansion potential - does the potential for expanded neonatal screening exist and, if so, for what disorders?

Reviewing the questions listed above provides a situational analysis of the major aspects of newborn screening for PKU. This information should provide an understanding of the complexities of the components necessary for an effective newborn screening system.

3. DEVELOPMENTAL GUIDELINES

It is essential that some forethought be given to the overall approach to development of an adequate and successful PKU screening programme prior to its establishment. The following guidelines are presented in order to provide an outline for this process:

- (a) Identify the sources of data available for each of the questions noted.
- (b) Compile existing data concerning the PKU burden, i.e., incidence, mortality and institutionalization.
- (c) Develop an inventory of the resources available for treating PKU patients. This inventory should include not only information about dietary product availability, but also a listing of treatment centres, qualified physicians, and laboratory services available.
- (d) Solicit the assistance of other professionals and nonprofessionals with similar interests in a successful screening programme and use this nucleus to begin fostering programme support and developing system procedures.
- (e) Develop a funding plan either through government, private, foundation or fee support or some combination of these.
- (f) Establish a working laboratory and secure specimen collection materials, prepare collection guidelines, and ensure transport for the specimens.
- (g) Educate the public and physician community.
- (h) Prepare an adequate follow-up system including register of diagnosed cases.
- (i) Institute screening on a pilot basis in order to establish the smooth functioning of the system.
- (j) Institute full-scale programme.

4. OBJECTIVES AND TARGETS

When considering objectives of a newborn screening programme for PKU, it is essential that proper treatment be available for the infants identified. It is impossible to have a goal of normal growth, development, and lifestyle if the means to reach this goal are not available. Any new screening programme for newborns should seek not only improved outcome for the disorder of interest but it should also look to the possibility of expansion to other disorders which could be approached with a similar strategy.

The primary goal of neonatal screening for PKU is to identify and treat infants whose inability to properly metabolize phenylalanine would otherwise result in mental retardation. To this end it is necessary to address several secondary objectives. These objectives are listed below:

Primary goal

Identify and treat neonates with PKU so that mental impairment does not occur.

Objectives

- (a) Screen every infant.
 - (i) test normal infants 1-3 days after birth.
 - (ii) test sick/premature infants before 7 days of age.
- (b) Confirm screening results with serum testing by 2 weeks of age.
- (c) Initiate dietary intervention by 3 weeks of age.
- (d) Assure stabilized normal phenylalanine levels by 4-6 weeks of age.

While admittedly the preceding objectives may seem ambitious at first glance, most well established PKU screening programmes function according to the schedule indicated. From a neuropsychological perspective, earlier stabilization produces improved outcome. Essentially no impairment can be expected in those patients under dietary control by one month of age.

Objective 1: Screen every infant

Despite the fact that PKU shows lower incidences in certain population groups, its autosomal recessive nature coupled with population intermixing makes it imperative that certain groups not be overlooked in the screening process. It becomes an exercise in futility to trace genetic backgrounds as a prescreening for such a relatively inexpensive screening test whose potential results can cause such dramatic outcomes.

- (a) Test normal infants 1-3 days after birth: all infants born in a hospital setting should be tested prior to release. If there is doubt as to the adequacy of protein challenge, a retest at 1-4 weeks should be considered. Arrangements must also be made for those infants born outside of the hospital setting to be screened. Midwife and other types of deliveries must not be overlooked in the overall scheme.

(b) Test sick/premature infants before 7 days of age - because of the necessity to begin treatment early for optimal outcome, sick or premature infants should be tested by 1 week of age. In view of the various complexities which often arise in the treatment of such infants, it is easy to overlook the possibility of a metabolic disorder such as PKU, thus a routine procedure for testing at 1 week is recommended as part of the standing orders in neonatal intensive care settings.

Objective 2: Confirm screening results with serum testing by 2 weeks of age

Infants exhibiting screening blood phenylalanine levels in excess of 8 mg/dL should be confirmed with serum tests immediately. Those whose values are between 4 mg/dL and 8 mg/dL may be rescreened, however, persistent elevations should be followed with serum testing. The possibility of tyrosinemia or other nonclassical forms of PKU, including bipterin defects, should not be overlooked.

Objective 3: Initiate dietary intervention by 3 weeks of age

Since dietary management is presently considered essential to positive outcome, it is necessary that a mechanism be in place whereby the appropriate supplemental food products are readily available to the affected individual. Some programmes have been effective in stockpiling cans of low phenylalanine formula for disbursement from a central warehouse. In other cases, parents have simply secured the necessary products directly from a vendor. In some developing nations, research laboratories have prepared substitute products for usage due to various economic and/or political reasons. In any case, it is incumbent upon the PKU screening system to have carefully considered a mechanism for dietary management. Wherever possible, nutritional/medical intervention should be included in this plan to assure optimal outcome.

Objective 4: Assure stabilized normal phenylalanine values by 4-6 weeks of age

Initial experiences with dietary management should be closely monitored with serum phenylalanine measurements until stabilization is achieved. It should be remembered that adverse affects can occur from too low a phenylalanine level as well as the reverse. Once stabilization is noted, a periodic schedule for blood monitoring should be established.

Other considerations

Having successfully instituted the preceding objectives, the screening programme will have taken a giant step towards its primary goal. A complete programme should track and monitor the patient throughout his life-time, if possible, and offer support and assistance should it become necessary. Such tracking is best done through a case registry and networking with other programmes.

As a long-term programme goal, the newborn screening PKU programme should set its sights on expansion to other disorders for which the system can serve as an administrative/technical nucleus. For instance, all newborn PKU programmes in the USA and Japan have now expanded to include screening for congenital hypothyroidism and many include other metabolic disorders as well. In order for

multiple disorder screening programmes to be economically feasible, however, it is almost a necessity that certain aspects of the programme be automated (e.g., specimen punching and data handling).

5. APPROACHES

Most newborn screening programmes for PKU have developed in one of two ways. Either there has been a legislated mandate to screen or there has been a pilot programme developed locally which has expanded to a much larger national programme. Either approach can be successful with adequate planning. The degree of success is directly related to the amount of planning involved.

It is perhaps easier to approach newborn screening for PKU through a legislative mandate in the sense that such mandates usually carry political and financial support. A review of the questions and answers obtained in the situational analysis can provide some of the resource information beneficial for providing the political persuasion necessary to encourage the legislative process. Unfortunately, nothing seems to catalyze the political process more than to have a politician whose life is directly affected by the problem of interest. Thus, knowledge of PKU individuals in the geographic area of concern and their relationship, if any, to persons in the political hierarchy can sometimes speed the enactment of enabling screening legislation. Where possible, such legislation should be carefully worded to allow expanded screening without the need for additional governmental intervention (i.e., allowing screening rules, regulations, and disorders of interest to be defined by a health commission or other suitable forum).

Legislation should require universal screening in order to be most effective since experience in systems where choices are allowed have sometimes led to abuses of the intent of the programme. This assumes, of course, that incidence in the population of interest justifies the screening need. An adequate funding mechanism is essential for screening, as with any health programme, thus any legislation should carry a means for obtaining financial support. Comprehensive cost estimates sufficient to allow for all aspects of the screening system must be provided to those in decision making positions. Items such as collection materials, postage, clerical support, analytical services (including laboratory equipment, reagents, personnel, and overhead), follow-up services, educational materials, dietary supplement, and treatment must not be overlooked. Similarly, cost savings for the government in reduced institutionalization expenditures and increased productivity of affected individuals must also be made available.

Politically active groups can be beneficial in presenting varying points of view and these should be carefully cultivated. As an example, parent groups are often very persuasive in their humanistic approach. Physicians can, of course, provide essential medical input.

Once legislatively mandated, it is safest to begin screening with a pilot programme in order to demonstrate the effectiveness and plausibility of the approach taken. Once the screening programme components are in place and their quality established, it is a simple matter to expand system operation.

The alternative approach to programme development also includes pilot programming. Initially the programme is begun on a small scale using local resources. The ultimate intent is to demonstrate screening effectiveness to the rest of the country. Examples of such programmes have been seen in hospitals where funding has been obtained from various sources in order to establish the feasibility of a larger newborn screening programme. It should also be remembered that other disorders of higher prevalency such as congenital

hypothyroidism may be coupled with screening for the less prevalent problem of PKU in order to show an overall increased cost effectiveness for screening.

Ethically there is always the question of patient consent for newborn screening. This may generally be approached in one of two ways. Either the parents may be informed of the testing and its reasons and then asked to consent to such testing (with appropriate signed documentation), or the parent may be informed and required to sign documentation only in cases of dissent. Both informed consent and informed dissent have been successfully employed by programmes in developed countries.

Because new medical programmes in developing countries are not always understood by the public, it is recommended that educational efforts be included in establishing the programme. Pamphlets for parental education must be developed at a very low educational level and be supplemented with interesting, simple diagrams and pictures. Programmes in Mexico have included the distribution of comic books to mothers for instance, while television presentations have been effective in Brazil. Whatever approach is undertaken, considerable effort will be necessary in order to gain public acceptance. Similarly it will be necessary to educate physicians, nurses and technicians as to proper specimen collection techniques. To this end, many different resources have been developed and should be secured from successful programmes in developed countries.

6. ACTIVITIES

Implementation of newborn screening for PKU involves the planning already outlined along with the implementation of these plans. Selection of a programme coordinator and an advisory committee are essential first steps. The programme coordinator should ultimately be responsible for development and management of the screening system and thus should have a background lending itself to these accomplishments. Public health experience coupled with extensive medical, nursing or laboratory knowledge in the area of PKU is preferable. The advisory committee should be composed of individuals knowledgeable in the field and able to lend practical as well as technical input to the decision making process. This group should function as technical advisers as well as programme proponents within the community. Development of the screening programme should follow a plan such as the one listed below:

Programme Development

- Month 1: Select programme coordinator who begins to develop goals and objectives, seeks financial support, and solicits input for committee member assignments. Make preliminary laboratory plans along with outlining specimen collection procedures.
- Month 2: Assemble advisory committee who provides advice concerning technical details of programme including time of collection, retest protocols, follow-up procedures, treatment, etc. Begin planning introductory educational materials for public and physician community.
- Month 3: Solidify programme ideas into workable system whose components have defined responsibilities. Plan pilot activities and arrange laboratory details.
- Month 4: Begin to secure laboratory equipment and collection forms ordered during Month 1. Continue developing educational materials. Plan start-up date for pilot programme and ensure specimen transport system is in place (i.e., mail, etc.).
- Month 5: Develop laboratory protocol and ensure clear delineation of responsibilities between specimen collector/submitter, laboratory, follow-up coordinator, and treatment provider.
- Month 6: Begin pilot screening. Develop treatment and thorough evaluation protocols with advisory committee input.
- Month 12: Complete educational materials and prepare for their distribution.
- Month 13: Distribute educational materials, hold training meetings, and expand programme to appropriate area depending on financial and technical constraints.

There are a great many details which must be added to this outline before a successful programme can succeed. Even if one assumes that a suitable laboratory can be developed and the necessary techniques transported from an established programme in a developed nation, there are often difficulties to be faced in obtaining laboratory supplies and collection paper, and in securing competent personnel. Specimen transport is often a problem and various

alternatives must be evaluated including mail, bus, truck, etc. The problems associated with "developed" screening programmes will be compounded in developing areas. Appropriate sample collection and patient tracking are perhaps the largest of these, thus, particular emphasis must be concentrated in planning these two programme facets.

It should be the responsibility of the specimen collector/submitter to document that collection has occurred, to know and exercise the appropriate collection and specimen submission procedures, and to assure that the properly collected specimen has been transported to the laboratory. Additionally, the receipt of results, either positive or negative, on each specimen submitted, should be documented.

The laboratory should document specimen receipt and adequacy, and perform the appropriate analysis. It should document acceptable quality control and report all results to the submitter (or designee) in a timely manner. All specimen results should be completed within a few days of specimen receipt and follow-up personnel notified of abnormal test results as quickly as possible. Documentation of result transmittal should be maintained by the laboratory.

Follow-up personnel must react to abnormal laboratory results with a time frame sufficient to have completed confirmatory testing and begun treatment by 1 month of age. This normally involves either a telephone or visitation system whereby receipt of abnormal laboratory findings initiates system actions and follow-up laboratory testing is performed within 1 to 2 weeks of the initial screen. Follow-up actions and their appropriate documentation must ensure initiation of treatment in those instances where it is appropriate. Thereafter, periodic documentation of patient well-being should be maintained as long as feasible.

Educational efforts have generally been a responsibility residing with follow-up programme personnel. However, a certain amount of laboratory oriented education is also necessary and therefore the laboratory often accepts a portion of this responsibility. The success of educational efforts in the laboratory may be easily monitored through specimen quality. Other education successes can only be assessed through a general increase in public awareness.

Overall quality of the screening programme should be an ongoing concern of all involved. It has been suggested that periodic blinded specimens should be sent through the system to check all of its components from specimen transport through follow-up. While an excellent theoretical idea, its practical application is often difficult to accomplish. Not difficult, however, is the blinded checking of laboratory procedures, and this should certainly be performed. Various external laboratory proficiency testing programmes exist throughout the world and involvement in at least one is essential.

7. MONITORING AND EVALUATION

Having defined the major goals and objectives of newborn screening for PKU, it becomes of interest to develop methods for monitoring and evaluating programme accomplishment. At any step along the way to programme implementation, it should be possible to determine the feasibility of a particular objective. While screening programmes for all neonates have been implemented in many locations worldwide, such screening becomes unfeasible if materials and services are unavailable. Self-evaluation of feasibility through preparation of a list of pertinent questions and their answers is perhaps the most effective way to evaluate programme development goals. If a goal is unattainable within a reasonable time period and with reasonable expenditure of effort, then it should be re-evaluated and perhaps redesigned. Examples of possible questions include:

- (a) Is a filter paper collection form available in the geographic area of interest and is it affordable?
- (b) Is agar available for the bacterial test (if used) or are chemicals available for the fluorometric procedure?
- (c) Is a specimen transport system available so that specimens are received in the laboratory within a few days?
- (d) Is there a financial mechanism available to pay for dietary treatment and/or other programme functions?
- (e) Is it possible to locate a patient after screening?
- (f) Can non-hospital births be expected to have a screening test performed?

Measuring the effects of the screening programme on society is possible through a more concrete approach. As a minimum, statistical tabulations should be kept of the numbers of infants screened and the number of tests with results in certain categories (e.g., <4 mg/dL, 4-8 mg/dL, 8-12 mg/dL, and >20 mg/dL). These results may be tabulated racially, geographically, etc., in order to provide information necessary to show false positive and true positive rates, scope of service activities, etc. Similar data should be kept on diagnosed cases for comparative purposes. If possible, developmental records should be kept on each diagnosed individual and compared to normal siblings or other suitable controls. Since the overall incidence worldwide for PKU is only about 1 in 15,000 births, statistical tabulations should be oriented toward keeping appropriate records over sufficiently large samples of data.

Evaluations of the component processes within the newborn screening system are necessary so that overall improvements in services may be realized. Collection processes may be evaluated through comparisons of specimens submitted versus total births, and satisfactory specimens received versus total specimens submitted. Educational methods related to professional training should be recorded and trends in specimen submissions (satisfactory versus unsatisfactory) should be monitored. Proficiency of the laboratory should be monitored through performance in external proficiency testing programmes. Such evaluations should be performed at least quarterly and any corrective actions should be documented. Times from specimen submission to result transmittal or receipt should be

monitored along with statistical tabulations of numbers of false positive results. Follow-up records should also be monitored with respect to documentation of actions and times for various actions to occur. The time to treatment is perhaps the most crucial statistic in the screening programme and its value is a measure of the system's success or failure.

Programme evaluation should also take into account any unplanned side effects. Such items as increased financial hardships on families who might be required to pay for dietary supplement, increased anxiety resulting from follow-up of false positive test results, cooperation (or lack thereof) from neonatal intensive care personnel, and time expenditures for tracking patients due to unsatisfactory specimens are but a few of the areas to be monitored.

It is essential that records being kept for programme evaluation purposes be described from the outset and that all programme personnel be aware of the need for uniformity in approach. Steps should be taken to prevent duplication of effort and results. The periodicity of these records should be assessed to ensure meaningful statistical results.

8. COSTS

Several studies have been made¹²⁻¹⁴ concerning the cost effectiveness of various strategies for newborn screening for PKU. Costs vary with location and each developing country must make its own determinations based on local economic factors. In addition to direct programme costs, it is important to calculate cost savings to the system realized by removal of the societal expense of caring for a mentally retarded child. Most calculations inadvertently omit the costs associated with specimen collection, long-term follow-up, and tracking of patients due to unsatisfactory first specimens. Additionally, comparative costs for routine second testing along with financial contributions to the economy resulting from productivity of otherwise nonproductive patients as adults might be included.

All of the studies referenced suggest a large cost-savings to society in general from neonatal PKU screening. The USA Office of Technology Assessment recently performed a more detailed cost analysis¹⁵ for various screening strategies involving PKU and congenital hypothyroidism, and this report is indicative of the myriad of calculations which may be involved in arriving at reliable cost figures. Health care costs and savings to society were calculated per 100,000 infants screened using 1986 US\$. These costs included the expense of blood specimen collection, laboratory detection, and medical treatment. In addition, cost savings from foster care, institutional care, and special education which would be averted by early detection were also included. This study concluded that, when compared to no screening, a substantial savings to the health care system is realized. When PKU screening was statistically coupled to screening for congenital hypothyroid screening, this combined screening resulted in a cost savings to the system of almost US\$100,000 per case detected. This study further concluded that the expense of specimen collection and laboratory detection were important cost components. Centralization of the laboratory component avoids duplication of fixed costs and highly trained personnel thereby causing a substantial cost reduction. Highest unit screening costs are realized in lowest volume situations.

Decisions regarding routine second testing of the entire population in order to detect those infants theoretically missed by screening too early are also cost dependent. Very few examples exist of PKU infants missed by screening too early despite the calculated expectancy of this occurrence¹³. It thus appears to be a very expensive proposition to perform second testings for PKU. This may not be true for congenital hypothyroidism where higher numbers of cases have been reported on second testing^{14,15}.

9. MANAGEMENT AND OBSTACLES

Management of the newborn screening system seems most effective when there is close cooperation between the programme coordinator, the laboratory manager, and the advisory committee. The importance of a procedural manual which defines component responsibilities including beginning and ending points cannot be over-emphasized. Such a protocol decreases duplication of effort, increases cooperative understanding, and serves to provide dynamic guidance which can be updated as programme needs change and as unexpected situations arise. Technical questions are usually best answered by one of the three components noted above and their ability to interact for the good of the system is essential. Development of a listing of key personnel at various specimen collection sites is a management tool which provides a quick reference for contact points in situations where follow-up actions are needed.

10. COLLABORATION

Success of the newborn screening programme for PKU is often the result of successful collaboration between similar programmes or between other components of the health care delivery system. On a local level, it is essential that knowledge and understanding of interrelated programmes provide a mechanism for sharing responsibilities wherever possible. With an already overburdened health care system, every effort must be made to take advantage of services already in place. On a broader plain, there is currently under development an International Society for Neonatal Screening and there already exists a Society for the Study of Inborn Errors of Metabolism. Involvement in these or similar organizations is strongly encouraged. Information exchange is essential in order to solve problems and improve services, and the mechanism exists through participation in these groups. Additionally, journal articles concerning newborn screening should not be overlooked.

Collaboration between laboratories currently exists through national and international proficiency testing and quality assurance programmes. The Centers for Disease Control in Atlanta, Georgia, USA, is central to these programmes in the USA while the German, French and Swiss Proficiency Testing Programmes cover many European countries and equally active programmes exist in Japan and Australasia (Australia and New Zealand). It is hoped that WHO will continue in its leadership efforts in this area by helping to establish a more comprehensive quality effort for all of newborn screening.

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II. General Principles for Formulation of Screening Programmes for
Phenylketonuria in the USA

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1. BACKGROUND

Newborn screening for inborn errors of metabolism began with the ideas expressed by Archibald Garrod in 1902¹. He originated the phrase "inborn errors of metabolism" which is the term still used in discussing newborn screening programmes today. In 1934, Folling² reported phenylketonuria (PKU) as an inherited metabolic disorder associated with mental retardation. Subsequently, testing for phenylpyruvic acid in wet diapers developed as a screening test followed by paper chromatography and other chemical procedures. When Bickel reported the effectiveness of his treatment technique in 1953³, there was renewed interest in mass screening and large programmes were established in Europe, New Zealand, and the USA, utilizing ferric chloride testing of urine specimens. This testing was not particularly successful due to the difficulty in obtaining specimens and the time involved before diagnosis.

In the late 1950s, Guthrie was involved in research in biochemical genetics related to mental retardation and in 1961 he developed a bioassay for phenylalanine. His report in 1963⁴ led to a proliferation of screening programmes throughout the USA. As these programmes developed, it was generally realized that mass screening was most cost effective and best controlled when performed in a large central facility. Thus, a number of state programmes were centralized at the state public health laboratory or in a regional laboratory central to several states. While most state legislatures reacted with legislation enabling the establishment of mandatory state newborn screening programmes, some elected to have voluntary programmes and some did not address the issue. Presently there are neonatal screening programmes for phenylketonuria in all of the fifty states, although there are still some states in which screening is voluntary and in which a central screening laboratory does not exist. The USA is one of the few countries which does not have a national newborn screening policy.

Both bacterial⁴ and fluorometric^{5,6,7} laboratory procedures have had demonstrated success in phenylalanine screening programmes. Properly controlled laboratories proficient in either analytical technique exist, and results of screening by both protocols appear comparable. Either technique is suitable for use with large numbers of specimens; is sensitive and specific to the analyte of interest; and, is economical. Additionally, collection of the appropriate specimen, heel stick blood on filter paper, causes minimal inconveniences to medical personnel, parents, and the infants screened. Once collected and transported, this specimen has the potential for analysis for other disorders, and indeed multiple newborn screening tests are routinely performed in many programmes.

This report is intended to offer guidance to those neonatal screening programmes in the USA which may be considering the improvement or expansion of their ongoing programme. Such programmes should be able to gain from the experiences of others and hopefully will benefit from the conciseness and suggested strategies of this report.

2. SITUATION ANALYSIS

Incidence of the disease

Phenylketonuria is an autosomal recessive disorder. Approximately one person in sixty carries the mutant, and the incidence both worldwide and within the USA is approximately 1 in 12,000-15,000 births. Even in the USA, incidence levels vary within geographic regions and among racial and ethnic groups. Rarely is PKU reported in Blacks or Ashkenazic Jews. While ethnic composition is probably the most predominant influence on the incidence of PKU, reviews of prevalence statistics require careful analysis due to differences in definitions of disorders and confusion between the terms classical PKU, hyperphenylalaninemia (HPA) syndromes, and co-factor variants. It is now recognized that all three are inborn errors of phenylalanine metabolism and share some common features. The course of each disorder, however, is distinctly different. The distinctions to be made between the three are adequately delineated elsewhere⁸ and will not be discussed here. It should be noted, however, that all three types of disorders can be detected in a properly established screening programme for phenylalanine.

Programme goals

It is the goal of every neonatal screening programme for PKU to detect infants with inborn errors of phenylalanine metabolism within the first few days of life in order to initiate dietary treatment as quickly as possible (no later than 3 weeks) so that mental impairment will be prevented. Mechanisms for attaining this goal may vary but certain primary components must exist for a successful programme. Efficient screening systems include: (1) informed and educated practitioners; (2) centralized laboratories with effective quality assurance; (3) well organized and persistent follow-up; and (4) adequate treatment resources. While these components generally exist within all areas of the country, their efficient, coherent management is often lacking. Strategies for such system development and maintenance are discussed in another section.

Testing protocols

In most states it has been helpful to have support of the state legislature in carrying forward the newborn screening system. Many different types of laws have developed over the years and have been cataloged.⁹ Likewise many different approaches to laboratory screening for phenylalanine exist. The American Academy of Pediatrics (AAP) has published genetic screening fact sheets¹⁰ noting that screening tests are usually from dried blood spots on filter paper taken from heel sticks, and that phenylalanine levels are measured by bacterial inhibition or fluorescent assays or, in some cases, by amino acid analysis (the latter procedure is utilized for confirmation). Sensitivity of the testing depends upon the level of phenylalanine used as a cut-off value and the age and protein intake of the patient at time of testing. It is generally agreed that a cut-off level of 4mg/dL will allow detection of PKU without unnecessarily burdening the system with numerous false positive results. Some laboratories, however, screen at a more conservative level of 3.5 mg/dL (particularly those using fluorometry) or even 2.0 mg/dL based on normal values determined in individual circumstances over statistically significant screening populations. While some programmes rescreen all newborns at 1 to 4 weeks of age, this type of rescreen has generally been productive only with detection of hypothyroid infants and not with PKU.

Programme management

Since the majority of patients with classical PKU exhibit screening phenylalanine levels in excess of 10 mg/dL, rapid serum confirmation of screening values in this range is recommended. Patients whose specimens exhibit values from 4 mg/dL to 10 mg/dL should also be retested, but whether the specimen is serum or another dried blood spot on filter paper varies widely among programmes. In all cases of persistent hyperphenylalaninemia, it is recommended that the possibility of cofactor variants be investigated. While classical PKU is not considered to be a life ending disorder, cofactor variants can cause childhood deaths. The treatment for PKU involves dietary management and supplementation with a low phenylalanine product. The cost of the dietary product is relatively expensive and presents a significant economic burden to the system. In many states, third party payers (insurance companies) provide a resource for assistance with this financial burden. Some states absorb this cost through a tax supported programme while others utilize income from a fee for PKU testing to support this cost. Still others pass this cost on to the family either fully or partially depending upon financial need. There is no single system which has been found to work in a majority of state programmes and there is no uniformity in insurance coverage.

Periodic laboratory monitoring of phenylalanine levels is helpful in maintaining appropriate dietary control and this service is often provided by the screening laboratory or a laboratory utilized by contract with a treatment centre. Therapy is best coordinated by a physician in conjunction with a trained metabolic nutritionist. State programmes often utilize the services of a metabolic treatment centre or tertiary care facility for primary follow-up of PKU patients. State programme coordinators and nutritionists offer a support core for centralized programme coordination. An advisory committee comprised of interested physicians, parent group representatives, and key programme administrators is also beneficial, not only for planning and advice, but also for political support as well as for the individual resources which each member individually offers. Often the PKU advisory committee is a subcommittee of a much larger genetics advisory committee.

Financial resources

Programme financial resources are an ever present problem. Most states allocate at least a portion of their general revenues to newborn screening. In many instances federal monies allocated for maternal and child health services are available for partial programme financing. A majority of states now utilize fee-for-service screening whereby specimen collection kits are sold to physicians, hospitals and midwives in order to finance the system. Unfortunately, costs of the entire newborn screening programme are often not fully calculated in these fees, leaving a well-funded laboratory programme without sufficient follow-up and treatment. Private foundation support is sometimes available as are grants from commercial sources.

3. OBJECTIVES AND TARGETS

AAP recommendations

It is the objective of every newborn screening programme for PKU that any infant with an inborn error of phenylalanine metabolism be detected and treated as soon as possible in its life so that mental impairment and other complications do not occur. It is, therefore, essential that a complete system be in place which assures specimen collection, laboratory analysis, follow-up, and treatment. If any one of these components is missing, the system falters and the ultimate goal becomes unattainable.

The Committee on Genetics of the AAP has addressed the components of an idealized screening programme for the persistent hyperphenylalaninemia (PHP), including PKU, and for congenital hypothyroidism in a set of recommendations.¹¹ These recommendations are primarily aimed at improving an already "developed" system. "An adequate screening programme for PHP ... should assure:

- (a) Total participation by the eligible population;
- (b) Notification of parents about newborn screening and their participation in this activity;
- (c) Reliable and prompt performance of the screening test;
- (d) Prompt follow-up of subjects with positive tests;
- (e) Accurate diagnosis of subjects with confirmed positive tests; and,
- (f) Appropriate counselling and treatment of patients."

State programmes

Since a national newborn screening programme does not exist in the USA, it is essential that state programmes be aware of the practice of others and that a sufficiently high standard of care be included in the state programme. In those states not subscribing to the centralized laboratory concept, it is important that state guidelines prescribe the level and type of service which must be provided so that all state residents receive essentially the same high level of screening care. In larger state programmes, guidelines to other areas of the newborn screening system should also exist for the same reason (e.g., for multiple treatment facilities, etc.).

Most state programmes operate with the intent of obtaining a suitable specimen for PKU testing within the first 3 days of life. For premature or stressed infants, this timeline is shifted to 7 days. Laboratory results on all infants (not just abnormal) should be reported to the specimen submitter within one week of collection. Follow-up serum confirmations should occur quickly so that affected infants are being treated by 21 days of age. Routine mailing of results is appropriate for normal values, however, abnormal or suspect values should be reported quickly by telephone and/or certified mail since these may constitute a medical emergency. Adequate documentation of all steps of the reporting/follow-up process must be maintained for legal liability reasons. Similarly, procedural manuals for all aspects of the screening system should be available and updated so that the beginning and ending point of responsibilities

for all components of the system are clearly identified. Such manuals should be realistic and usable rather than idealized in content.

4. APPROACHES

Most newborn screening programmes for PKU in the USA developed through legislative mandates during the 1960s as a result of Guthrie's work, and interest by the National Association for Retarded Citizens (NARC) and the Children's Bureau of the Department of Health and Human Services. Economic justification for these programmes was based on the cost savings to states in decreased institutionalization of retarded persons who would presumably be detected and their retardation prevented by screening programmes. Since a national screening programme was not forthcoming, programmes developed individually but with a common goal. Unfortunately not all areas of the country viewed the need for screening in the same manner and thus some of the approaches were better funded and supported than others. To date three states (Maryland, North Carolina and Vermont) remain without mandatory screening laws although all states have well developed programmes in operation. There remain some problems, however, in the ability of some states to attain the idealized programme previously listed in the AAP guidelines and, thus, the remainder of this section will centre around implementation of the components of the ideal programme.

Participation

In order that no infant be missed by the screening network, it is preferable that legislation be in place which makes newborn screening for all newborns mandatory. Legislation should allow test selection to be established through the State Health Commission or other appropriate body without necessary legislative action so that other disorders for which screening might be appropriate by the same mechanism (i.e., heel stick blood collected on filter paper and mailed to a screening laboratory) could be more easily added to the ongoing programme. Exemption from screening should be provided only for religious reasons or in dire medical circumstances and documentation of refusal should be maintained for liability protection.

Education

An educational component of the newborn screening system should be provided. Education should involve medical practitioners including physicians, nurses, midwives, and hospital administrators, as well as the general public (particularly new or expectant mothers). Public education should include general awareness information designed to explain the disease, its need for detection, and how the testing programme functions. Such information should be provided at about fifth grade educational level and should be concise. Practitioner education, on the other hand, should emphasize proper timing and collection of specimens for testing along with clear delineation of protocols and responsibilities in meeting these obligations within the system. Similarly, protocols and responsibilities for follow-up of presumptive positive results should be clearly defined. Nutritional material along with outcome information should be available to patients and their families if PKU is detected. Preparation of various types of educational materials are possible including pamphlets, manuals, videotapes, and sound-slide programmes. Educational responsibility most logically rests with the administrative portion of the system although in some instances laboratory involvement has been quite heavy and effective in this regard.

Testing

Prompt, reliable testing is essential. Experience has shown that a centralized laboratory testing at least 30,000 specimens annually is the most efficient and effective laboratory strategy. When fewer specimens are tested, failure to recognize true positive results have been encountered and less efficient technical resource management is realized. For future test battery expansion, laboratory programmes should consider automation of specimen punching and analysis to the extent economically possible. Computerized information management is the rule rather than the exception, and programmes should take advantage of systems already functioning rather than waste time redeveloping such technology.

Specimen collection should follow the suggestions of the National Committee for Clinical Laboratory Standards (NCCLS)¹² and collection forms should be in computer format wherever possible. Consideration should be given to barcoded serialization of collection forms for future computer possibilities¹³ and filter paper used should be labelled with lot number and expiration date. It has been suggested that improperly timed and/or collected specimens be rejected for analysis for liability reasons¹⁴ and that through this mechanism coupled with practitioner education, better specimens and thus better testing reliability can be obtained. In general, an adequate filter paper specimen is one in which sufficient circles are filled and thoroughly saturated so that an appropriate analytical attempt can be made for each and all of the tests required of the programme (i.e., 1 circle for 4 or less tests, 2 circles for 8 or less tests, etc., when using punch index equipment). A properly timed specimen for PKU is one collected after an infant has received protein nourishment for at least 24 hours. This timing requirement varies, however, for other disorders, and should be modified by the programme to meet the needs of the system as a whole. Proper timing and specimen quality is the responsibility of the submitter and should not require unnecessary monitoring by other programme components such as the screening laboratory. The screening laboratory should only be concerned with proper analysis and result reporting related to the specimen submitted.

The screening laboratory should review specimens for adequacy and ensure itself of properly standardized and controlled analytical protocols. For either the bacterial inhibition or fluorometric procedures, 1/8 in. (3 mm) unautoclaved disks may be used. Addition of penicillinase to the agar formulation will eliminate some of the problems resulting from antibiotic interferences.¹⁵ Following initial analysis to select potentially abnormal specimens, a second analysis should be performed in duplicate from new disks punched from the original specimen as a quality control procedure. Bacterial testing on these repunches is generally best performed on autoclaved specimens which give slightly better definition of bacterial growth and eliminate most of the inhibition problems caused by antibiotic interferences. External proficiency testing should be required and frequent quality assurance specimens should be analyzed. In general it is agreed that a phenylalanine result of 4 mg/dL or higher is indicative of a potential problem and that the patient requires follow-up blood analysis of some type. Confirmatory serum phenylalanine analyses should be the recommended protocol when initial screening results exceed 8 mg/dL. In the abnormal range below this value, either a repeat filter paper or serum specimen is appropriate at the option of the programme. Due to the relative infrequency of screening values of 4 mg/dL or higher, many programmes suggest serum confirmation of all elevated values. Persistent elevations of phenylalanine should also require evaluation for cofactor variants

as suggested earlier in this report. The newborn screening system should provide for the necessary confirmation and variant testing required as part of the programme.

Follow-up

In order to ensure that laboratory results indicative of PKU are properly transmitted to the appropriate health care provider so that confirmation of results and initiation of treatment result, a formal follow-up system is essential. Result notification by the laboratory should be to the submitter or his designee on every specimen received and should also be to the programme administrative person responsible for follow-up at the system level on all abnormal results. Documentation of these transfers should be kept. The follow-up protocol should exist in written form and include a requirement for telephone contact (with documentation) of the patient's health care provider (HCP) on all abnormal results. Written notification should also be made and properly documented (e.g., certified mail). A mechanism must also exist for following through on result confirmation in a timely manner so that all children affected with PKU reach treatment before 21 days of age. In instances where notification of the appropriate follow-up HCP is not possible, public health nurses or other resources (local law enforcement, etc.) should be utilized to complete the confirmation and initiate care. Follow-up begins with transmittal of abnormal results from the laboratory and ends with documentation of patient treatment. Most states have established registers of diagnosed patients and perform annual tracking so that patients may be advised of advancements in treatment and so that assistance may be offered in later years to females contemplating pregnancy. A national computerized tracking system is currently under development which may aid in assisting more mobile patients. It is the responsibility of the follow-up system to assure that the patient has access to dietary supplementation as well as primary health care.

Diagnosis

Completion of the appropriate diagnostic work-up should be the responsibility of the HCP with assistance from follow-up personnel if necessary. Serum analyses should be available from an appropriately controlled, reputable laboratory. In some instances this service is provided by the state health agency while in others it is available through the treatment centre. In either case, results must be available within a brief time span so that treatment is not delayed. Cofactor variant analysis should not be overlooked. These services are currently provided through federal funding at one specified laboratory on a national level. Details concerning this testing are available through the Bureau of Maternal and Child Health and Resource Development in Washington.

Treatment

Treatment is most effective when accomplished through a combination of medical and nutritional efforts. Periodic visits with a physician knowledgeable in treating metabolic defects coupled with serum phenylalanine monitoring for dietary compliance and dietary support from a trained nutritionist are optimal. Serum monitoring services are often provided by the state health agency but wherever obtained, must be appropriately controlled for quality. Parental education is paramount for successful dietary management and formation of a parental support group should be encouraged whenever possible. If dietary

products cannot be supplied to the affected individual(s) by the programme for economic or other reasons, the programme must bear the responsibility of assisting the patient, to whatever extent possible, in obtaining outside assistance for this purpose. While it is the goal of follow-up to ensure that patient treatment is begun by 21 days of age, it is the HCP's responsibility to obtain decreased phenylalanine values and dietary compliance by 4-6 weeks of age.

5. ACTIVITIES

Staff selection

In order to effectively accomplish the desired goals of PKU screening, a strong newborn screening system must be implemented which requires that certain essential activities be initiated. It is important that system advocates be available to assist with obtaining public and political support as well as to advise on programme direction. A strong programme coordinator responsible for defining system component functions and responsibilities should formulate an advisory committee for external support. This committee should be involved in decisions regarding such questions as screening protocol, definition of responsibilities, and follow-up and treatment methodologies. It should not be given authority to make specific technical or administrative decisions but rather should be utilized for general advice. Its make-up should include interested physician(s) specializing in genetic or metabolic practice, a consumer advocate, and any others considered to have appropriate backgrounds relative to the desired committee accomplishments. Public health experience coupled with extensive medical, nursing, or laboratory knowledge in the area of PKU is preferable and out of hospital births (midwives) should not be overlooked.

Legislation

Most screening programmes in the USA began with legislation enacted in the 1960s and this legislation has either remained unchanged or has been "patched" to allow expanded testing over the years. Each programme should periodically review the appropriateness of its legislative mandate in view of current standards of practice and should effect necessary changes. Likewise the local rules and/or regulations relating to such legislation should be evaluated and changed if necessary. For liability, as well as public health reasons, it is essential that well developed and well thought out legislation and rules be in place which authorize the appropriate newborn screening system. If a fee-for-service is utilized then it is important that the fees generated be available to directly support the screening system including, not only laboratory testing, but also follow-up personnel and treatment including expenses related to dietary supplementation.

Programme manual

While most programmes have bits and pieces of procedures in place for many of the activities comprising the screening system, many do not have a comprehensive programme procedural manual. In order to eliminate communication difficulties and to aid in "cementing" the components into a coherent newborn screening system, it is strongly suggested that a detailed comprehensive newborn screening procedural manual be developed. This manual should realistically define each components responsibilities and interactions between the components. It should include a step-by-step protocol for each portion of the programme and should be periodically updated as changes occur. This documentation of procedures is especially important in legal matters where protocols and procedures will invariably be challenged.

Education

Education is also an important programme activity often overlooked. Without proper education of both users and providers of newborn screening services, the overall system slows in its effectiveness. Practitioners must be educated regarding timing and collection of specimens in order to prevent costly delays in retesting and diagnosis. Likewise parents or potential parents need information about testing and its outcome in order to make informal decisions concerning the necessity for testing. Where staff is not available for personal educational involvement, pamphlets and audio visual material can be extremely useful. Resources available from other newborn screening programmes should be investigated and used wherever possible.

Quality assurance

Overall quality of the screening programme is an ongoing concern of all involved. Where practical, periodic blinded specimens should be sent through the system to check all of its components from specimen transport through follow-up. Where this is not practical, a blinded check of the laboratory procedure should still be implemented since testing of this nature is relatively easy and is routine in most quality laboratories. External proficiency testing of the laboratory is essential and several programmes for such testing exist including the primary programme at the Centres for Disease Control.

If the USA is to develop a national screening system, then these same concerns must be applied at a different political level. Such a policy is possible and its implementation for PKU screening would be fairly simple in view of the high quality of the programmes already in place. The problems to be addressed would most likely be related to methods of programme financing (fee or appropriation), necessity for financial assistance with dietary supplementation, and programme quality assurance.

6. MONITORING AND EVALUATION

Effective programme management involves the monitoring and evaluation of both programme components and their objectives. As an aid to providing meaningful statistical information for self evaluation, programmes should develop a mechanism for annually obtaining follow-up data on each patient diagnosed. Some programmes have utilized return postcards with limited questions which are sent to patients, physicians, or metabolic specialist advisors. The questions posed must be brief, pointed and allow quick responses, otherwise the return percentage is less than optimal. Smaller programmes have obtained this information through telephone contacts.

In order to measure the effectiveness of the screening protocol, statistical tabulation of numbers of specimens received, numbers reported in various ranges (e.g., <4 mg/dL, 4-8 mg/dL, 8-12 mg/dL, 12-20 mg/dL, and >20 mg/dL), and numbers diagnosed (tabulated according to range of initial result). Additionally results may be analyzed racially, geographically, etc., in order to provide information necessary to evaluate programme goals. If possible, developmental records should be kept on diagnosed individuals and compared to normal siblings or other suitable controls.

Compliance with the prescribed procedure(s) for specimen collection may be easily evaluated through statistical comparisons on a submitter basis. Comparisons of specimens submitted versus hospital births give feedback on programme availability and compliance. A review of unsatisfactory specimens tabulated by type of problem give a measure of the effectiveness of submitter education. Monitoring transit and follow-up times and comparing time to treatment can assist in locating other system difficulties. The time to treatment is the most crucial statistic in assessing system effectiveness and will be utilized by others to measure the success or failure of newborn screening for PKU.

Overall programme evaluation must not overlook other societal impacts. Such items as financial hardships to families who might be required to pay for dietary supplement or long-term care medical/laboratory services, impact of anxiety resulting from false positive follow-up, cooperation (or lack thereof) from neonatal intensive care personnel, and time expenditures for tracking patients due to unsatisfactory laboratory specimens need to be assessed.

It is essential that programme records of the type mentioned above be kept for programme evaluation. The items of interest should be chosen and described carefully so that all personnel involved are aware of the necessity for keeping such records. Steps should be taken to prevent duplication of effort and results. The periodicity of all record keeping should be appropriate for meeting a desired goal and should not be useless data for meeting this need.

7. COSTS

Several studies regarding costs associated with newborn screening exist^{16,17,18}. As might be expected, costs vary with location and services provided. When making cost calculations (cost justifications) it is important to calculate cost savings realized by removal of the societal expenses related to caring for a mentally retarded child. Calculations must also include costs associated with specimen collection, long-term follow-up, and tracking of patients due to unsatisfactory first specimens.

Cost analysis generally suggests a substantial cost saving to society from neonatal PKU screening. A recent USA Office of Technology Assessment¹⁹ is perhaps most comprehensive in its approach. In this report, health care costs were calculated per 100,000 infants using 1986 US\$. When PKU screening was statistically coupled to screening for congenital hypothyroidism screening, this combined screening resulted in a cost saving to the system of almost US\$100,000 per case detected. It was further concluded that the expense of laboratory collection and laboratory detection were important cost components, and that centralization of laboratory components avoids duplication of fixed costs and highly trained personnel which results in system-wide cost savings. Highest unit screening costs are realized in lowest volume situations.

Routine second testing of the population in order to detect cases theoretically missed by screening too early in the infant's life is also a cost concern. There are very few examples of PKU infants missed by early screening despite the calculated expectancy of this occurrence²⁰. It thus appears to be a very expensive proposition to perform routine second screening for PKU alone. This may not be true of congenital hypothyroidism^{21,22}.

In order to cover the cost of newborn screening programmes, various states have instituted a fee-for-service plan. Usually monies are collected through the sale of filter paper collection kits. In some cases, stamps to be placed on the filter paper form are sold while in other cases, submitters and/or patients are billed as specimens are received. In instances where patients are unable to pay, an alternative scheme is necessary. State fees vary from US\$6.00 to US\$25.00 for collection kits and many submitters add a handling fee to cover their administrative costs. Unfortunately, many state fee schedules are adjusted to cover only laboratory costs and do not provide financial relief for other portions of the newborn screening system. Any fee imposed should be sufficient to support all aspects of the programme for which it was developed and the programme should have specific authority for use of the funds recovered. Other alternatives to a fee-for-service exist. Included in these are complete or partial state support, partial federal support (block grant funds, etc.), private support, and, in some cases, partial commercial support (reduced costs for formula, etc.). It is prudent to explore all avenues of financing rather than to depend on a single strategy.

8. MANAGEMENT AND OBSTACLES

The management of most successful screening programmes is most effective when close cooperation and communication occur between the programme coordinator, the laboratory manager, and the advisory committee. Workable protocols throughout all areas of the system are mandatory and their smooth transition from initial patient contact through diagnosis and treatment is essential. A written procedural manual not only aids in the overall management process but also provides documentation of standard of care should questions in this area arise.

Most obstacles to the screening processes evolve because of communication difficulties. Specimen collection problems can arise from technical difficulties related to specimen collection procedures or filter paper quality, however, most difficulties in this area remain the fault of a lack of understanding by one party as to the requirements of another. Guidelines for determining specimen adequacy, etc., must be carefully communicated to the person(s) responsible for specimen collection. There are also problems encountered in communicating results to submitters so that patients may be followed with additional tests. It is important, therefore, for the programme person making contacts with practitioners to establish a network of contact individuals at the submitting offices. Good programme management and communications can overcome most obstacles.

9. COLLABORATION

Most state health systems encompass a multitude of multifunctional programmes. Often these programmes have service arms which can be used in coordination with other programmes to accomplish mutually useful goals. It is, therefore, important that services available to Women Infants and Children (WIC), Crippled Children's Services (CCS), and other similar programmes be fully utilized by newborn screening. Formula (dietary supplement) and medical care for infants in newborn screening are often available through these programmes. Likewise, close coordination with public health nursing programmes for follow-up and third party payers for additional cost reimbursement are important.

Collaboration with other programmes having similar goals and objectives in other states offers the opportunity to discuss and attack similar problems with greater resources. Communication through published articles, newsletters and professional societies should not be overlooked. For laboratories, results of proficiency testing programmes provide helpful feedback concerning quality. In the future, it is anticipated that a national group similar to the International Society for Neonatal Screening will provide a forum for collaboration in this area.

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