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Urinary Screening Tests in the Prevention of Mental Deficiency

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A substantial number of genetically determined biochemical disorders in infants and young children produce mental deficiency and serious ill health in early life. If these diseases are detected promptly, effective therapy can be instituted to prevent the development of mental defect, or, where no treatment is presently available, the parents can be given appropriate genetic counselling so that the birth of further affected children can be prevented.

Eight simple urine screening tests are described which have proved useful in the early detection of metabolic disorders in apparently healthy infants. These tests can easily be performed by a physician or nurse without special training or elaborate equipment. The attention of general practitioners, pediatricians and public health physicians is directed to the real possibilities for preventing some forms of mental deficiency through the routine use of screening tests on urine and on blood.

Un nombre important de troubles biochimiques d'origine génétique qui surviennent chez des nourrissons et de jeunes enfants provoquent de la déficience mentale et un très mauvais état de santé au début de la vie. Si ces maladies peuvent être décelées précocement, il est possible d'instaurer un traitement efficace pour prévenir l'apparition des troubles mentaux ou, si tel traitement n'existe pas, de donner aux parents des conseils judicieux sur la génétique de façon à éviter la naissance éventuelle d'autres enfants tarés.

L'article décrit huit simples tests urinaires qui se sont révélés utiles pour la détection précoce de troubles métaboliques chez des nourrissons par ailleurs apparemment sains. Un médecin ou une infirmière peut facilement procéder à ces épreuves, même s'ils n'ont pas reçu une formation spéciale et s'ils ne disposent par d'appareils compliqués. On attire l'attention des omnipraticiens, des pédiatres et des médecins hygiénistes sur les possibilités qu'offre l'emploi courant des tests de dépistage urinaire et sanguin pour prévenir certaines formes de déficience mentale.

DURING the last decade, many exciting advances have been made in our knowledge about the nature of a number of genetically determined metabolic disorders which lead to mental deficiency or which cause serious illness and early death in infancy and childhood. Substantial progress has been made in the study of the primary biochemical error in these diseases, and in many instances accurate diagnostic techniques are now available, and successful forms of treatment are at hand. It is doubtful, however, whether enough use is being made of this new knowledge by members of the medical profession.

At least seven biochemical disorders which cause mental deficiency or neurological and other serious clinical manifestations in early life are now treatable. Prompt diagnosis and careful therapy of these disorders can be expected to prevent or ameliorate the mental defect, and in some will prevent death or serious illness in childhood. The beneficial effects of the low-phenylalanine diet in phenylketonuria, of a milk-free diet in galactosemia, and of thyroid replacement therapy in several forms of cretinism have been repeatedly documented. The neurological damage associated with maple syrup urine disease, which leads either to death in infancy or to severe mental defect, can be prevented by the administration of a diet low in the branched-chain amino acids, leucine, isoleucine and valine.[1-3] Wilson's disease, which when untreated progresses to cirrhosis, neurological disease, loss of intellect, and premature death, responds well to early and continued treatment with D-penicillamine.[4-5] The failure to thrive, hypoglycemia, coma and convulsions encountered in infants with that rare disorder, hereditary fructose intolerance, can easily be prevented by a diet free of fructose and sucrose.[6] Finally, homocystinuria, a recently discovered disease which causes mental defect, dislocation of the ocular lenses, skeletal malformations, and intravascular thromboses, responds well to a diet low in methionine and supplemented with cystine, if this regimen is instituted early in infancy.[7, 8]

Several additional diseases which involve errors in amino acid metabolism may soon be treatable. Tyrosinemia, a disorder probably due to an absence

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of *p*-hydroxyphenylpyruvic acid oxidase in the liver, leads to cirrhosis and renal disease which is often fatal in infancy; it has been found to respond favourably to a diet low in phenylalanine and tyrosine.[9-11] In cystathioninuria, the abnormal urinary excretion of cystathionine can be corrected by administration of large doses of pyridoxine.[12-14] The enzyme cystathionase is not absent in this disease but is inactive; its activity can be increased by high tissue concentrations of pyridoxal phosphate. It is possible that the diagnosis of cystathioninuria early enough in infancy and the prompt institution of pyridoxine therapy might prevent the mental defect which is usually present. There is also suggestive evidence that the mental deficiency found in histidinemia and in hyperglycinemia might respond, respectively, to diets low in histidine[15] and in leucine.[16]

There is an additional group of genetically determined biochemical diseases characterized by the development of mental deficiency, for which no treatment is available and there is little prospect that a successful therapy can be developed in the near future. Early diagnosis of these disorders is almost as important as for those conditions which are now treatable. If the diagnosis can be established by laboratory methods in early infancy long before mental retardation or characteristic physical signs appear, suitable genetic counselling of the baby's parents may prevent the birth of further defective children in that family. Hurler's syndrome and the cerebro-oculo-renal syndrome of Lowe are good examples of diseases in this category.

In Canada, as in most other countries with high standards of medical care, there is a serious discrepancy between the availability of new scientific techniques for the diagnosis and treatment of biochemical disorders leading to mental deficiency and the actual employment of these techniques in medical practice. A serious effort to find a metabolic disorder causing mental defect has been made in only a minority of our institutionalized defectives. Only a fraction of the newborn infants in a few Canadian provinces are now being screened for phenylketonuria by the Guthrie test.[17] With the exception of a few medical centres, little or no effort is made to detect in young infants the several other metabolic disorders which demand prompt treatment, if mental defect and other serious illness are to be avoided.

The primary purpose of this paper is to present details of a group of urine screening tests which in our laboratory have proved useful for the detection of metabolic disorders in infants and children. These tests are so simple that they can be performed by any physician or nurse without special laboratory facilities or previous training. They are not intended to make a final diagnosis, but rather to pick out from the mass of apparently normal infants those few who require careful investigation for metabolic disorders.

An additional purpose of this communication is to suggest to physicians interested in public health the need for a more aggressive attitude in establishing procedures for routine screening of infants' blood for biochemical disorders. These blood-screening tests cannot be carried out in the physician's office or in the well-baby clinic, but are practical for a central laboratory.

DESCRIPTION OF URINE SCREENING TESTS

Collection and Handling of Urine Specimens

Screening tests for possible metabolic errors should be performed only on freshly collected urine or on urine that has been frozen. Ten millilitres of urine is ample for the performance of all the tests described below, and the tests are reliable even after the urine has been stored many months in the deep freeze. Urines that have been frozen should be thawed and shaken well to assure adequate mixing before being tested. No preservatives should be added. Urine specimens that have been wrung out of a wet diaper, or contaminated with feces, or have been allowed to stand for hours at room temperature are unsuitable and should never be tested. Experience in actual pediatric practice has shown that with good office organization and encouragement of mothers, proper urine specimens can readily be obtained from young infants.

Equipment Required for Screening Tests

The following equipment is needed for performance of the tests described below:

Small test tubes (13 mm. outer diameter x 100 mm.).

Racks to hold small test tubes.

A pan for immersing rack in boiling water, and a suitable source of heat.

1 ml. serological pipettes.

Disposable Pasteur capillary pipettes, about 15 cm. long, and rubber bulbs to fit.

The following additional equipment is convenient, but not essential:

Centrifuge, clinical or laboratory.

15 ml. conical heavy-duty glass centrifuge tubes.

Timer clock.

Preparation and Storage of Reagents

A practising physician or a public health nurse who wants to carry out these chemical screening tests on urines could have the necessary reagents prepared, as described below, by any well-equipped hospital laboratory. Most of the reagents could probably also be obtained from and prepared by a pharmacist. Some of these reagents must be stored in the refrigerator when not in use, and the need for refrigeration is indicated with the description of each test.

I. FERRIC CHLORIDE TEST

The reagent is made by dissolving 1.0 g. of ferric chloride ($FeCl_3.6H_2O$) and 1.0 g. of ferrous am-

monium sulfate ($Fe(NH_4)_2(SO_4)_2.6H_2O$) in 100 ml. of 0.02 *N* hydrochloric acid. The reagent appears to be stable at room temperature indefinitely.

The test is performed by placing 1 ml. of the ferric chloride reagent in a test tube, adding 10 drops of urine, and mixing by shaking. The resulting colour is observed within two or three minutes. A green colour indicates the presence of phenylpyruvic or imidazolepyruvic acid. With this version of the ferric chloride reagent, *p*-hydroxyphenylpyruvic acid is not detected. The appearance of a purple or purple-brown colour indicates that the patient has recently ingested aspirin.

A positive ferric chloride test makes it likely that the patient has phenylketonuria or histidinemia, and requires further confirmatory tests on blood and urine. Contrary to what is often stated, the ferric chloride test as described above, and carried out on fresh urine, is a highly sensitive and accurate screening method for phenylketonuria. Urines of phenylketonuric infants usually give positive tests within the first two weeks of life.

II. CYANIDE-NITROPRUSSIDE TEST

(a) 5.0 g. of sodium cyanide is dissolved in 100 ml. of water.

(b) 5.0 g. of sodium nitroprusside ($Na_2Fe(CN)_5NO.2H_2O$) is dissolved in 100 ml. of water.

Both compounds decompose gradually in aqueous solution, and should therefore be stored in the refrigerator. For best results, fresh sodium cyanide solution should probably be made up once every month. Sodium cyanide is highly toxic; it should be appropriately labelled, and kept carefully away from exploring children.

The test is performed by placing 1 ml. of urine in a test tube and adding 0.4 ml. (about 12 drops) of the sodium cyanide solution. The tube is agitated to mix, and allowed to stand for five minutes at room temperature. Then one drop of the sodium nitroprusside solution is added, and the tube is shaken. An immediate pink to beet-red colour indicates a positive test.

A positive cyanide-nitroprusside test indicates that the urine contains an excessive amount of cystine or homocystine. Paper chromatographic studies will then show whether the patient has cystinuria, is heterozygous for cystinuria, or has homocystinuria. This screening test was strongly positive in a homocystinuric infant on the fourth day of life.[7]

III. QUALITATIVE BENEDICT'S TEST

(a) 17.3 g. of cupric sulfate ($CuSO_4.3H_2O$) is dissolved in 100 ml. of water.

(b) 173 g. of sodium citrate and 100 g. of anhydrous sodium carbonate are dissolved in 700 ml. of boiling water. The solution is filtered, and the volume of the filtrate is adjusted to 850 ml. with water.

(c) The citrate-carbonate solution (b) is poured into a large beaker, and with constant stirring the copper sulfate solution (a) is slowly added to it. The volume is then adjusted to 1000 ml. with water. The qualitative Benedict's solution is stable indefinitely at room temperature.

The test is performed by pipetting 1 ml. of the Benedict's solution into a test tube, adding three drops of urine, mixing, and heating the tube in a boiling water bath for not less than five minutes. A yellow, orange or red precipitate indicates the presence in the urine of an abnormal amount of glucose or another reducing sugar. If the test is positive, paper chromatography for sugars should be done, and this procedure can detect galactosemia, hereditary fructose intolerance, pentosuria and, of course, diabetes mellitus.

IV. NITROSONAPHTHOL TEST

(a) 2.63 *N* nitric acid is prepared by adding one part of concentrated nitric acid to five parts of water.

(b) 2.5 g. of sodium nitrite is dissolved in 100 ml. of water.

(c) 100 mg. of 1-nitroso-2-naphthol is dissolved in 100 ml. of 95% ethanol.

Reagents (b) and (c) must be kept in the refrigerator, while the nitric acid reagent is stable at room temperature.

The test is performed by placing 1 ml. of the 2.63 *N* nitric acid in a test tube. One drop of the sodium nitrite reagent is added, followed by 0.1 ml. (or 10 drops from a Pasteur pipette) of the nitrosonaphthol reagent. The tube is agitated to mix, and, without undue delay, three drops of urine are added and the tube is again agitated to mix. The development of an orange-red colour within two to five minutes indicates a positive test, while persistence of the original yellow colour indicates a negative test.

A positive nitrosonaphthol screening test indicates that the urine contains excessive amounts of one or more of the following compounds: tyrosine, *p*-hydroxyphenylpyruvic acid, *p*-hydroxyphenyllactic acid, or *p*-hydroxyphenylacetic acid. A positive test suggests that the patient may have tyrosinemia, and indicates the need for more definitive tests of blood and urine.

V. NINHYDRIN TEST

1.0 g. of ninhydrin is dissolved in 500 ml. of 95% ethanol. The solution should be stored in the refrigerator when not in use.

The test is performed by placing 1 ml. of the ninhydrin reagent in a test tube. Three drops of urine are added, and the tube is agitated to mix. The tube is allowed to stand at room temperature and is examined after two and five minutes. The presence of a distinct blue or purple colour, particularly at two minutes, indicates that the urine

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may contain an excessive amount of one or more amino acids.

This urinary screening test is positive in many different diseases involving aminoaciduria, but is especially useful for detection of generalized aminoacidurias. Positive urines should be examined further by two-dimensional paper chromatography for amino acids. A very concentrated urine may give a false-positive ninhydrin screening test. Conversely, a very dilute urine may contain a significant excess of one amino acid and yet fail to yield a purple colour at five minutes.

VI. DINITROPHENYLHYDRAZINE TEST

1.50 g. of 2,4-dinitrophenylhydrazine is dissolved in 400 ml. of methanol, to which is then added 100 ml. of 6 *N* hydrochloric acid (one part each of concentrated hydrochloric acid and water). After the dinitrophenylhydrazine is allowed to dissolve, any visible debris is filtered off, and the reagent is stored in a *brown bottle* in the refrigerator. The reagent must not be exposed to light or heat when not in use.

Before the dinitrophenylhydrazine test is performed, a drop of urine is placed on an Acetest tablet (Ames Co. of Canada, Toronto, No. 2381). If a purple colour appears, indicating the presence of acetone, there is no point in performing the dinitrophenylhydrazine test, since acetone in the urine will react positively. If the Acetest is negative, 1 ml. of *clear* urine is placed in a test tube. The supernatant of centrifuged urine is ideal for this purpose, but if a centrifuge is not available, clear urine can be carefully pipetted from the top of a container without disturbing the sediment below. Three drops of the dinitrophenylhydrazine reagent are added to the urine; the tube is agitated to mix, and is then allowed to stand for 60 minutes at room temperature.

The appearance of a light yellow, cloudy precipitate in the tube indicates a positive test and suggests the need for a more detailed examination of the urine for alpha-keto acids. This urine screening test is positive in untreated patients with phenylketonuria, tyrosinemia, maple syrup urine disease and histidinemia.

VII. CETYLTRIMETHYLAMMONIUM BROMIDE TEST

(a) 1.0 *M.* sodium citrate buffer, pH 5.75, is prepared by first dissolving 210 g. of citric acid monohydrate in 500 ml. of water. 150 ml. of 20 *N* sodium hydroxide is then added; the solution is mixed well and cooled to room temperature. The pH is then adjusted (on a pH meter) to 5.75 by the careful addition of 20 *N* sodium hydroxide (about 15 ml.). The buffer is then diluted to a final volume of 1000 ml. with water.

(b) 25 g. of cetyltrimethylammonium bromide is dissolved in about 900 ml. of the above 1.0 *M.* citrate buffer, warming as necessary to facilitate dissolving. The solution is then diluted to a final volume of 1000 ml. by adding further 1.0 *M.* citrate buffer. The reagent is probably stable indefinitely at room temperature.

The cetyltrimethylammonium bromide test for mucopolysaccharides is performed by adding six drops of the cetyltrimethylammonium bromide reagent to 1 ml. of *clear* urine in a test tube. The tube is agitated to mix and is examined after 10 minutes at room temperature. As with the preceding test, and the following test as well, urine free of sediment must be used.

The appearance of a cloudy precipitate after the addition of the reagent to urine constitutes a positive test. This suggests that the patient may have Hurler's syndrome (gargoylism) or some other disorder of mucopolysaccharide metabolism.

VIII. SULFOSALICYLIC ACID TEST

20 g. of sulfosalicylic acid is dissolved in 100 ml. of water. The reagent is stable indefinitely at room temperature.

The test is performed by adding three drops of the 20% sulfosalicylic acid to 1 ml. of *clear* urine in a test tube. A cloudy precipitate indicates an abnormal amount of protein in the urine.

This test is likely to be positive in untreated galactosemia and in Lowe's syndrome (cerebro-oculo-renal syndrome). When it is positive it is also useful as an indication of many forms of renal disease.

DISCUSSION

Table I lists a number of genetically determined biochemical disorders which can be detected in infants and children by the simple urinary screening tests that have been described. Table I also indicates which tests may be expected to be positive for each disorder.

For three of the diseases in Table I the urine tests are diagnostically valid only under certain conditions. A negative Benedict's test rules out galactosemia only if the infant is actually ingesting a diet which includes milk or milk products. This test will exclude the rare disease, hereditary fructose intolerance, only if the infant is receiving a formula containing sucrose, or is old enough to be eating fruits and sweets. The ninhydrin test is not likely to detect the gross aminoaciduria found in Wilson's disease until the end of the first decade of life, or later, at which time symptoms of the disease may already be appearing. A negative ninhydrin test on an infant's urine does not exclude the enzymatic defect which underlies Wilson's disease.

Individually, all of the diseases listed in Table I are uncommon, and the odds are small that any *one* of them may be encountered by a physician in his practice. On the other hand, the chances are great that every physician who cares for infants and children will eventually encounter one or more patients suffering from some disease in this group. Accurate detection of these diseases early in life,

TABLE I.—SOME DISEASES DETECTABLE BY URINE SCREENING TESTS

Disease	Ferric chloride	Cyanide-nitroprusside	Benedict's test	Nitrosonaphthol	Ninhydrin	Dinitrophenyl-hydrazine	Cetyltrimethyl-ammonium bromide	Sulfosalicylic acid
Phenylketonuria*	+				±	+		
Maple syrup urine disease*					+	+		
Galactosemia*			+		+			+
Hereditary fructose intolerance*			+					
Homocystinuria*		+			±			
Cystinuria*		+			+			
Wilson's disease*					+			
Tyrosinemia**			±	+	+	+		
Cystathioninuria**					±			
Histidinemia**	+				±	+		
Hyperglycinemia**					±			
Hypophosphatasia**					±			
Argininosuccinic aciduria					±			
Hyperlysinemia					±			
Citrullinemia					±			
Cystinosis			±		+			
Hartnup disease					+			
Lowe's syndrome			±		+			+
Hurler's syndrome							+	

*Effective treatment available.
**Disease probably treatable.

followed by appropriate treatment where this is possible, and by genetic counselling where no therapy is available, can lead to a significant reduction in infant mortality, and to a small but important reduction in the number of children who become mentally defective.

The argument is often heard that it is not worth the trouble to perform a urine screening test for a rare metabolic disease on an apparently healthy infant, because the chances are so slim that the infant might have that disease. If we were to follow this argument to its logical conclusion, we might reasonably discontinue certain portions of the physical examination normally carried out by a careful physician when he performs a well-baby examination. The chief reason, for instance, for routine measurement of an infant's head circumference with a tape measure on each office visit during the first year of life is to enable the physician to detect promptly unduly rapid or unduly slow growth of the head. These findings might indicate either an early hydrocephalus or a premature cranial synostosis amenable to neurosurgical correction. A careful physician palpates the abdomen of the infant to whom he administers well-baby care, perhaps primarily to search for a neuroblastoma or a Wilms' tumour, prompt surgical removal of which might save the baby's life. But there are probably many fewer infants with surgically correctable hydrocephalus, premature closure of the sutures, and abdominal tumours than there are infants with serious biochemical disorders. Yet no one would seriously propose discontinuing measurement of head circumference or careful palpation of the abdomen as a routine part of the physical examination of healthy infants.

In 1966 there will probably be fewer cases of tetanus in Canada than there will be new cases of phenylketonuria. Why then should we not try as hard to detect cases of the latter disease and to prevent the resultant mental deficiency as we do to see that every Canadian child is given tetanus toxoid to prevent the occasional development of tetanus after accidental injury? The argument that a physician should not feel an obligation to carry out a simple laboratory test for a biochemical disorder which leads to mental deficiency simply because the disease is rare is not valid.

On whom should urine screening tests be carried out, and when? We believe that every infant should be tested, regardless of apparent good health, and that testing should ideally be done when the infant is 10 days to two weeks old. The testing of urine collected in the newborn nursery will not rule out some of the diseases listed in Table I, since the infant must have consumed enough food and lived in an extrauterine environment long enough to accumulate the metabolites which provide diagnostic clues to the underlying enzyme-deficiency disease. Routine testing of infants' urines for the first time at the age of six weeks or two months is too late. By that time irreparable brain damage may have occurred in the infant with phenylketonuria or homocystinuria, and the infant with maple syrup urine disease may already have died of his disease. The time-honoured routine of examining infants in the newborn nursery and then not seeing them again until they are one to two months of age should be modified in view of new diagnostic measures and treatments available to the physician. Ways can be found to carry out the tests we have described at the optimum time without increasing the frequency of well-baby visits or increasing the time spent by physicians and nurses. For instance, it might be more sensible to examine infants first in the newborn nursery, then in the physician's office or well-baby clinic at the age of 10 days or two weeks, and after that to see infants next at the age of two or three months when immunizations could be started.

Besides carrying out urine tests routinely on all infants in the second or third week of life, these tests should also be used on infants or children of any age who fail to thrive, whose mental development is unduly slow, or who show any signs of neurological disease. Every child who is mentally retarded certainly should have the benefit of these simple tests. These tests may provide clues which can lead to the establishment of an accurate diagnosis in a retarded child. Although it will probably be too late to benefit that child, nevertheless a younger sibling, or potential siblings not yet born, may certainly be helped.

Who should perform the urinary screening tests which have been described? We believe that every physician who cares for infants, whether he is a general practitioner or pediatrician, should be prepared to screen infants in his office for treatable metabolic diseases. The cost to the physician for the minimal equipment and the reagents needed to perform these tests at least once on each of the infants he might treat in an entire lifetime in practice would probably not exceed $100. The physician who claims that performing these tests is too much

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work, or that they will require too much of his or his office staff's time, is probably trying to care for too many patients. The obvious answer for the overworked physician who wants to give his patients the best and most modern medical care available is to take on an associate. It should be obvious, also, that these urine screening tests could equally well be performed by public health nurses working in a well-baby clinic, or by nurses at a centralized facility following home visits to young infants.

Most urine specimens tested will prove entirely negative, and parents can be reassured that laboratory tests confirm the impression that their baby is in excellent health. When a urine specimen gives one or more positive tests, further laboratory investigation should be undertaken promptly. Sometimes this can be done practically in the laboratory of any good community hospital. The performance of two-dimensional paper chromatography for urinary amino acids, or of one-dimensional paper chromatography for urinary sugars, is not too difficult for the laboratory of a hospital of 100-bed capacity or larger. For more complex diagnostic procedures, frozen urine or plasma, or perhaps the patient, can be sent to a large hospital or university medical centre. Once a definite diagnosis has been established, and appropriate treatment has been started, if this is possible, the infant can and should be returned to the care of the original physician. The latter should be able to carry out the treatment of the infant in the home community and should be capable of interpreting the disease to the family and of providing them with suitable genetic counselling. In appropriate cases, additional advice and guidance usually can be obtained from specialists at medical teaching centres.

PUBLIC HEALTH AND BLOOD SCREENING

Responsibility for the early detection of metabolic diseases which lead to mental deficiency should not rest solely with the individual practising physician. Public health authorities have an opportunity to establish community facilities to carry out one of several available blood screening tests. The Guthrie test,[17] which measures phenylalanine concentrations in blood and is an effective method of screening for phenylketonuria, is in use now in several Canadian provinces. Its great advantage is that it is performed on capillary blood which can be obtained easily from infants before discharge from the newborn nursery. Blood is blotted on to filter paper, and the papers are later mailed to a central laboratory where many blood specimens are assayed simultaneously by a simple bacterial culture inhibition method. The serious disadvantage of the Guthrie test is that it screens for only a single metabolic disorder, where many should be looked for.

Two relatively simple techniques have been described which screen the blood of newborn infants for a much wider variety of diseases leading to mental deficiency. Both involve one-dimensional paper chromatography of blood to search for increased concentrations of a number of amino acids. The method developed by Efron *et al.*[18] utilizes for chromatography the same spots of blood which are submitted on filter paper for the Guthrie test. The method developed by Scriver, Davies and Cullen[19] utilizes serum for amino acid chromatography. Blood specimens are collected by heel puncture in capillary tubes, the tubes are mailed to a central laboratory where they are centrifuged to separate the sera, and the sera are applied directly to paper chromatograms.

Use of one or the other of these two chromatographic screening procedures requires the support of public health authorities to set up a central laboratory for testing blood specimens sent in from physicians caring for newborn infants. Such a laboratory might use one of these methods in addition to the Guthrie test or instead of it. The blood screening tests fail to pick up those metabolic disorders which do not involve a primary error in amino acid metabolism. On the other hand, they are valuable in diagnosing certain disorders which are not detected by the urine screening tests previously described in this paper—for instance, hyperprolinemia and hydroxyprolinemia.[20, 21] In a disorder such as maple syrup urine disease, where severe brain damage occurs rapidly in untreated patients, a paper chromatographic test on blood obtained in the newborn nursery can result in earlier diagnosis than a urine screening test performed one or two weeks later, and therefore earlier treatment may significantly preserve the patient's intelligence.

It is important to remember that a negative blood screening test obtained on the fourth or fifth day of life does *not* rule out the presence of a treatable metabolic disorder. If the newborn infant is breast-fed, or if for some other reason the infant has consumed little milk at the time of discharge from the nursery, the concentration of a particular amino acid in blood may not yet be sufficiently high for detection of an incipient metabolic disease. Blood screening tests ideally should be performed on each infant just before discharge from the newborn nursery, and this procedure should be followed by urine screening tests at the age of two weeks. The current use of the Guthrie test in some Canadian provinces and American states, where infants are tested only in the newborn nursery, is both unimaginative, in that only one disease is tested for, and hazardous, in that some cases of phenylketonuria will be missed. In Massachusetts, where the Guthrie test is correctly employed and attempts are made to obtain a second blood specimen from every infant after discharge from the newborn nursery, cases of phenylketonuria have been picked up by the repeat test which were missed on the original test.[22]

Organized medicine and provincial and metropolitan public health agencies might well consider whether they are currently doing all that they should to prevent mental deficiency. Although considerations of expense should not be paramount when it comes to preserving the health of children and guaranteeing optimal development of the human mind, it is clearly bad economics not to make adequate screening tests available to the entire community. In Canada at least one phenylketonuric infant is born for every 20,000 live births. Prompt diagnosis of this one case and effective treatment with a low-phenylalanine diet can prevent development of severe mental defect which would almost certainly require the child's permanent placement in a provincial hospital for mental defectives. The cost to the public for hospital care of such a defective for the lifetime of a phenylketonuric is now at least $200,000. Thus, the financial savings entailed in the detection in early infancy of a single case of phenylketonuria could pay for an effective provincial screening program for a wide variety of metabolic disorders for several years.

SUMMARY

Eight simple urine screening tests are described which can easily be performed by a physician or a nurse in an office setting without expensive laboratory facilities. These tests detect the minority of apparently healthy infants who nevertheless have a genetically determined biochemical disorder which will later result in mental defects, or in serious or fatal illness in early life. Since for a number of these metabolic disorders treatment is now available that can result in the child's growing up in normal health and with normal intellect, systematic testing for these disorders becomes an essential part of good preventive health care for infants. Whether the conditions discovered are treatable or not, the urine tests permit early and rational genetic counselling of parents. Emphasis also is placed on the advantages of blood screening techniques for the early detection of several important metabolic diseases. These tests must be carried out in a central laboratory on blood specimens collected elsewhere by physicians and nurses, and it is suggested that public health authorities and the organized medical profession should take greater initiative in setting up such facilities.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

COMPARE HIM WITH MR. ENO

All this nostrum and proprietary business depends upon secrecy, upon the zeal and assurance of the advertising proprietors and upon the gullibility of the purchaser. Patent medicines, unless they contain some dope, are short-lived.

A very instructive story is that of Dr. Warburg, of Vienna. About the middle of last century Warburg's solution of quinine was very highly esteemed in many countries. The Austrian Imperial Health Board ordered it to be kept in all the pharmacies of the empire; English physicians in India averred that by it they effected cures they were unable to effect by the simple drug. But unfortunately for him sufficient pressure was brought to bear to induce him to divulge his recipe, and at once its sale fell off and shortly almost altogether ceased. Everybody said: Oh, is that all—quinine with a little aloes and aromatics. He died a comparatively poor man, and yet his combination had perhaps a certain amount of value. Compare him with Mr. Eno, of Eno's Fruit Salts, who died worth six million of dollars, or the self-dubbed Professor Holloway, vaunting the efficacy of his pills, and his ointment of turpentine and beeswax. He left money sufficient to found colleges for women and asylums for lunatics. Remember also Dr. Morrison and his pills of gamboge, colocynth, squills, cream of tartar and ginger—a pill such as my conscience and my knowledge of the action of drugs never would allow me to prescribe—and yet physicians, we are told, ordered them surreptitiously, and the English public swallowed them freely believing his wild statement, "that all diseases arise from one cause and therefore require but one medicine; it follows that if Morrison's pills do not cure no other medicine on earth will, and infallibility belongs to God". In his day pills and statements were not sugar-coated but were made strong. Our modern proprietary humbugs cover their chaff with a little wheat and take care that their nostrums please the eye, tickle the palate, and gently stimulate the imagination by some suggestive name or statement.

It is also in my opinion reprehensible, and I do not think this is too strong a word to use, for the physician to countenance proprietary preparations of even official drugs. For the pharmacist the fact that he is obliged to keep such an innumerable array of proprietary preparations on his shelves, together with the special tablets and pills of not one but many large manufacturing houses, must demand a large cash outlay; an outlay for which the pharmacist must recoup himself out of the pockets of our patients. Such recouping eventually reacts against the profession.—A. D. Blackader, *Canad. Med. Ass. J.*, 6: 582, 1916.