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GENERAL PRACTICE

Case-Finding in Phenylketonuria

I. Report of a Survey by the College of General Practice of Canada

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ABSTRACT

In the years 1961 and 1962 the College of General Practice of Canada undertook a survey to detect infants with phenylketonuria. Routine urine tests for phenylketonuria were performed on all babies in a number of practices and records were kept. On a total of 4334 babies 6247 tests were carried out. Physicians' comments and the ages at which first, second and third urine tests were performed are reported. In an 18-month period, three confirmed and two probable cases of phenylketonuria were discovered.

Although it is not necessarily the most efficient method of case-finding, it is recommended that testing the urine for phenylketonuria should be a part of routine baby care.

SOMMAIRE

En 1961-1962, le Collège de Pratique Générale du Canada entreprit de relever les cas de phénylcétonurie. Chez tous les enfants qui sont passés dans un certain nombre de pratiques privées, on procéda couramment à la recherche de phénylcétonurie et on en garda trace sur des fiches. On fit 6247 épreuves sur un total de 4334 bébés. L'article rapporte les commentaires des médecins sur l'âge des sujets au moment où on procéda au premier, au deuxième et au troisième dosage urinaire. Sur une période de 18 mois, on mit à jour trois cas formels et deux cas probables de phénylcétonurie.

On conseille de procéder couramment à la recherche urinaire de phénylcétonurie, bien que ce ne soit pas nécessairement la méthode de diagnostic la plus efficace.

THERE is considerable evidence that a low phenylalanine diet will prevent mental deterioration in patients with phenylketonuria.[1-3] Although much has still to be learned about the optimal use of this diet, it now seems clear that the younger the baby is when he starts the diet the more intelligence he will retain.[1, 4] The importance of early diagnosis in this disease cannot be overstressed. The present communication is a report of a case-finding survey undertaken by the College of General Practice of Canada. Subsequent communications will be concerned with the Guthrie test and other case-finding programs.

METHODS

In November 1960 the Central Research Committee of the College of General Practice of Canada asked the members of the College to participate in a phenylketonuria case-finding program.[5] The request was made in the form of a letter published in *The Canadian Medical Association Journal* and in the *Bulletin* of the College. A short article on the essential features of phenylketonuria was published at the same time.

A few months later the 2000 members of the College were sent a copy of both the letter and the article, in English and French, made up in the form of a brochure. Members were requested to start routine urine tests for phenylketonuria on all babies who came under their care. Details of spot-testing the urine with ferric chloride,[6] and the use of Phenistix (Ames Co. Ltd.), were provided. The brochure was accompanied by a plastic squeeze bottle containing 10% ferric chloride and a booklet

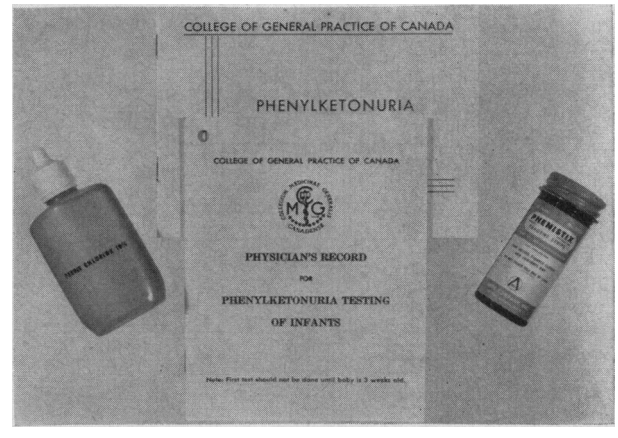

Fig. 1.—Test kit for phenylketonuria issued to the members of the College of General Practice.

From the Department of Pediatrics, Queen's University, Kingston, Ont., and the College of General Practice of Canada.
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in which to record results (Fig. 1). Six months later a second letter was sent out together with a bottle of Phenistix* and a second copy of the above-mentioned booklet. It was requested that the results of all tests should be recorded and returned to the College. A year later, in January 1963, a final letter was sent out containing a short questionnaire and requesting return of the record booklets.

RESULTS

Number of Babies Tested

A total of 146 booklets were returned to the College containing the test results on 4334 babies. About 65% of the babies were tested once, 26% were tested twice and 9% were tested three times. A total of 6247 tests were reported (Table I).

TABLE I.—NUMBER OF BABIES TESTED FOR PHENYLKETONURIA AND TOTAL NUMBER OF TESTS CARRIED OUT

	Number of babies tested			
	Once	*Twice*	*Three times*	*Totals*
Number of babies.....	2798	1159	377	4334
Number of tests.....	2798	2318	1131	6247

In addition, from comments on the questionnaire, it was clear that tests had been carried out on at least another 1300 babies but the records of the results of these were not available.

Age of Testing

The age of the baby at the time of the test was recorded in 3988 instances. A few babies were tested in the first and second weeks of life, but the commonest age for the first test was four to six weeks. The great majority of the babies were given their first test by the age of two months (Fig. 2). Most of the babies who were tested twice were given their second test between the ages of one and four months and those tested three times were given their third test between the ages of three and five months.

Physicians' Comments

Two hundred and eighty-one replies to the questionnaire were received. Thirty members of the College indicated that they had no babies in their practices, that they had retired, that they had not received test materials, or that they were unable to co-operate for other reasons. Most of the remaining doctors were continuing to test routinely for phenylketonuria and had had no difficulty in incorporating the test into their routine baby care. Several doctors found that it was easy to forget to do the test and others remarked on the high frequency of dry diapers!

At least 55 doctors reported that parents had asked that the child be tested for phenylketonuria. Estimates of the frequency of such requests varied

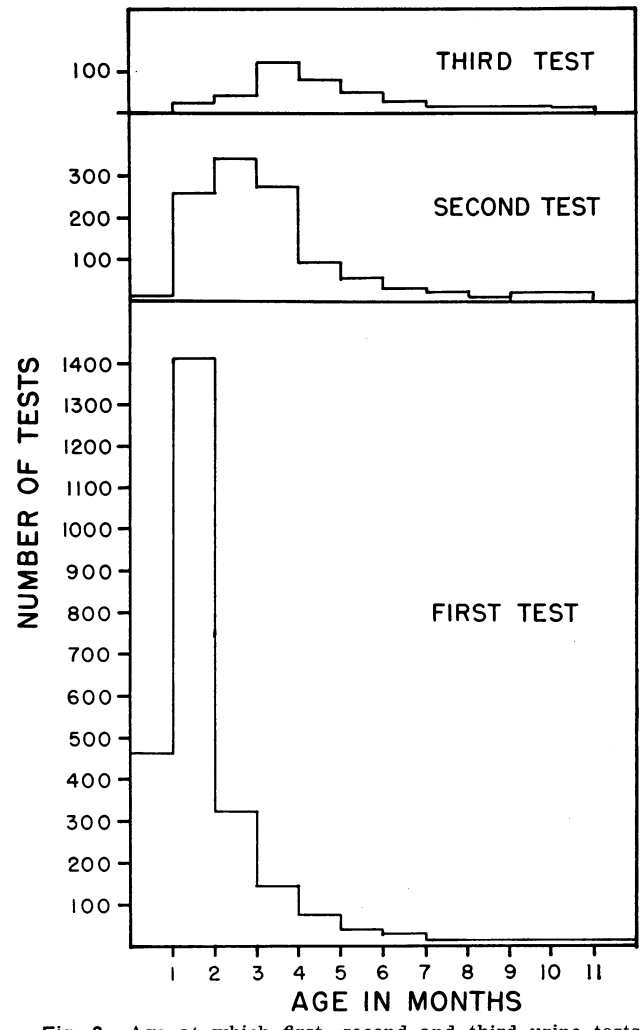

Fig. 2.—Age at which first, second and third urine tests for phenylketonuria were carried out.

from a few mothers to 80%. The mothers had apparently become aware of the problem through radio, television and the local associations for retarded children. One or two doctors felt that testing routinely for phenylketonuria might alarm the mothers, but most reported that the parents either accepted the procedure as "just another test" or else were appreciative and pleased about it.

The members were asked to express their preference for ferric chloride or Phenistix. Of 220 doctors who replied, 87 preferred ferric chloride and 133 preferred Phenistix. The usual reasons for preferring ferric chloride as a test agent were that it was cheaper and easier to use than Phenistix. Some complaints that the ferric chloride stained the diaper were received but these were minor or negligible, or were accepted as "a normal hazard of the test". The mothers appeared to be satisfied if they were forewarned that a permanent stain would result. Some doctors noted a white precipitate in the ferric chloride solution and concluded that the material deteriorated rapidly. The usual reasons given for preferring Phenistix were that it was easier to use and that there was no staining of the diaper.

*Kindly supplied by the Ames Co. of Canada.

Very few doctors reported difficulty in interpreting the results of either type of test. Babies in whom the test was equivocal were retested after a few days and one or two were referred to a pediatrician.

Cases of Phenylketonuria

Three cases of phenylketonuria were discovered by routine urine tests and the diagnosis was confirmed by the finding of elevated blood phenylalanine levels. A fourth child was found to have a positive urine test; a presumptive diagnosis of phenylketonuria was made and dietary treatment was started without confirmatory blood tests (Table II).

TABLE II.—CONFIRMED AND SUSPECTED CASES OF PHENYLKETONURIA DISCOVERED BY ROUTINE URINE TESTS

Case number	*Age positive test found*	*Urine test used*		*Blood phenylalanine level*	*Province*
		Ferric chloride	*Phenistix*		
1	4 weeks	—	+	Raised	Ontario
2	2 months	+	—	Not measured	Ontario
3	4 months	—	+	Raised	Ontario
4	2 years	—	+	Raised	Alberta
5	?	+	—	Not measured	Saskatchewan

Another child, in an outlying part of Ontario, had a retarded elder brother in an Ontario Hospital School. Later studies showed that this brother did not have phenylketonuria. The baby was followed from birth and the urine was tested daily with ferric chloride. At the age of two months the urine test became green. The child was changed from breast feeding to an evaporated milk formula and the green reaction of the urine increased in intensity. A presumptive diagnosis of phenylketonuria was made and a low phenylalanine diet was started. Following this the urine became negative to ferric chloride. The baby was maintained on this diet until the age of six months, when arrangements were made to admit him to hospital to confirm the diagnosis. Just before this was done the child developed a respiratory infection and died unexpectedly 48 hours later. At autopsy, four hours after death, the tracheobronchial tree contained aspirated stomach contents and this was considered to be the cause of death. The bladder urine was negative when tested for phenylketones. This evidence, taken as a whole, strongly suggests that the patient had phenylketonuria but the diagnosis was not proved.

DISCUSSION

Three confirmed and two suspected cases of phenylketonuria were discovered by this survey in the course of 18 months. In accordance with the experience of others,[7-9] this demonstrates that cases of phenylketonuria *can* be found by routine urine testing. It is possible that the babies might have been diagnosed earlier if the pattern of testing with regard to age had been "shifted to the left" (Fig. 2); that is, if the babies had had their first test in the first rather than the second month of life, their second test in the second month and so on. This is by no means certain, however, since the age at which phenylpyruvic acid first appears in the urine in infants with untreated phenylketonuria is very variable and may be delayed up to four months.[10]

The number of cases of phenylketonuria found in this survey appears high. Unfortunately there is no way of verifying this statement, since the total number of babies tested is unknown. Reports were received on about 5600 (4334 + about 1300) babies. If this were the total number of babies tested, the incidence of phenylketonuria would be from 1 in 1100 to 1 in 1900. This is about 10 to 20 times higher than that usually estimated.[11] This seems unlikely, but it also seems unlikely that the total number of babies tested was 10 to 20 times larger (i.e. 56,000-112,000) than the sample reported. The unsupported inference is that, in fact, the incidence of phenylketonuria in North America is higher than the 1 in 20,000 to 1 in 40,000 usually cited. This conclusion has been reached by others on different grounds.[12, 13]

Although this survey has demonstrated that phenylketonuria can be diagnosed by routine urine tests, it should not be concluded that this is the most efficient method of case-finding. Several examples of phenylketonuria are known in which the urine had been screened in early life and found to be negative.[14, 15] This is the reason for advising repeated tests on every child. Furthermore, because of the common pattern of well-baby care and the inevitable proportion of babies who do not have wet diapers at the time they attend the doctor's office,[6, 14] the diagnosis in those infants who are excreting phenylpyruvic acid may be unduly delayed. This is of importance because in most cases the maximum amount of brain damage in untreated phenylketonuria occurs in the first month or two of life. Lastly, an unknown proportion of babies do not come under routine medical care after the immediate newborn period. Some hospitals (referred to by doctors in their replies to the questionnaire) have tried to solve the problem by testing the urine of all newborn babies prior to discharge from hospital. This routine might detect the occasional case of phenylketonuria, but most cases will be missed because at this age (five to seven days) the majority of phenylketonuric babies are not yet excreting phenylpyruvic acid in the urine. Other case-finding programs will be discussed in a subsequent communication.

SUMMARY AND CONCLUSION

The results of a case-finding survey for phenylketonuria conducted by the College of General Practice of Canada are reported. Three new cases of phenylketonuria were found in an 18-month period by routine urine tests. It is concluded that urine testing for phenylketonuria should be included as a routine in well-baby care.

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CASE REPORTS

Treatment of Epidermolysis Bullosa Dystrophica by Alpha Tocopherol

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EPIDERMOLYSIS bullosa is a chronic skin disease which is usually hereditary and is characterized by the development of bullae, especially on skin areas that are easily traumatized. Treatment of this condition has always been unsatisfactory and still is; fortunately, the disease is rare.

The bullae that develop contain a fluid which is usually clear amber but can be hemorrhagic or purulent. These vesicles enlarge many times when light pressure is applied to them. As they age, the bullae develop into painful crusted ulcers which leave atrophic scars on healing. Usually, before healing has taken place completely, new crops of bullae appear in the area and a vicious circle of healing and breakdown continues for months or years. The skin has little or no elastic tissue and is usually hypersensitive. The mucous membranes and conjunctivae may be involved. The victim's expectation of life is decreased. Treatment up to this time has consisted of the local application of ointment and the use of steroids and multiple vitamins. To the author's knowledge, alpha tocopherol has never been used before in the treatment of this condition, as in the following case.

A 14-year-old boy was admitted to the Ontario Hospital School, Orillia, on January 16, 1961, with extensive lesions of the skin, mucous membranes of the mouth, throat and conjunctivae. The condition of his skin, when the dressings were removed, can scarcely be described. It is difficult to image a more unpleasant sight, compounded of blisters of all sizes, scabs, scars and bloody purulent discharge. Approximately 10 nursing hours daily were required to care for this patient. He was placed in a warm plain water bath for half an hour twice daily before removal of his dressings. Apart from his dermal lesions he appeared to be in relatively good health. The staff were confronted with the prospect of having to care for this patient for years in the state described above or worse.

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Personal experience in the treatment of a chronic varicose ulcer with vitamin E induced me to make a trial of alpha tocopherol in this boy's disease. The varicose ulcer referred to healed readily, has not recurred, and the patient has been active since. It seemed that what was so useful for one type of ulcer might be helpful in this particularly discouraging condition. So far as we could find in the literature and in conversation with dermatologists, alpha tocopherol had never been used in the treatment of such a patient. The general appearance of the patient's face suggested vitamin deficiency in spite of the multivitamins he had long been receiving.

The boy was the youngest of six siblings. The fifth, who was 10 years older than our patient, was reported to have the same type of skin disease.

Our patient was born on July 2, 1946, in Ontario. Six hours after birth it was noted that his skin was abnormal. Bullae soon appeared and some became pustular. His nails began sloughing off. He was admitted to a pediatric hospital on July 26, 1946, and the diagnosis of epidermolysis bullosa dystrophica was confirmed. Soon the mucous membranes of his mouth became ulcerated. Many forms of treatment were used. He remained in the hospital until he was transferred to a home for incurable children on February 2, 1955, at nine years of age. He remained there until his transfer to the Ontario Hospital School, Orillia, on January 16, 1961.

Ulceration was most marked over and around areas of his body which were exposed to friction. His hands, forearms, and the distal half of his arms were covered with confluent, fiery red ulcers in various states of breakdown and healing. His hands were clenched and encased in a membrane with only the tip of his left thumb protruding. He could move his fingers. Radiographs showed reasonably normal bone formation. There was a moderate degree of flexion of both wrists. His feet, ankles and knees, and other areas were covered with massive ulcerating patches. Pressure points on his back and shoulders were ulcerated. His mouth had ulcers at the corners, and the oral orifice was greatly contracted. Initially he was unable to open his mouth wide enough to allow the examiner to see the back of his throat, because this was painful. Later,