

## *Problems affecting the community*

### Population screening

BARBARA E. CLAYTON

*From the Hospital for Sick Children, Great Ormond Street, London*

Screening an apparently healthy population for metabolic disorders raises many ethical problems. It is all too easy to undertake screening of poor quality and if it is to be of a high standard it requires excellent organization, a high order of collaboration between clinicians and laboratories, and a very clear idea of the purpose of the operation. Comprehensive guidelines for genetic screening were published by the Institute of Society, Ethics and the Life Sciences in 1972, and this group too emphasized the need to be clear about the goals served by screening and the benefits to be obtained by the individuals and their families. There was particular emphasis on the need for informed consent, the protection of the subject when relatively untried testing procedures are used, and the provision of counselling. In particular, there was anxiety about maintaining the right of privacy of the individual and the group considered that there is always a risk that information obtained from genetic screening may be misused or misinterpreted.

It is necessary to differentiate clearly between screening programmes of a service nature and those which are really research projects. Whatever test is used should be acceptable to the subject and be economic to carry out. In addition the test should not miss too many cases, ie, the rate of false negatives should be low, nor should too many false positives be obtained since such findings generate anxiety in healthy families and also require effort and money to sort them out. Some of these problems have been discussed recently by Wilson (1973). In many parts of the world population screening has been initiated by laboratory workers as a result of techniques which they have developed—and as a laboratory worker myself I fully appreciate the desire to search for disorders which are of such biochemical interest. Screening, however, must be a close partnership between the laboratory and the clinician because subjects can easily be harmed if they become aware that an ‘abnormality’ has been found or if treatment which may at best be unnecessary and at worst be harmful, is initiated.

#### Screening for Phenylketonuria

Phenylketonuria (PKU) is a good example of a condition for which it is worth screening since it is one of the few causes of mental retardation for which effective medical treatment is available. When the care of a child with PKU has been good from the early weeks of life, adequate intellectual development takes place (Clayton, Moncrieff, and Roberts, 1967; Baumeister, 1967; Fuller and Shuman, 1969; Hudson, Mordaunt, and Leahy, 1970; Kang, Sollee, and Gerald, 1970; Koch, Dobson, Blaskovics, Williamson, Ernest, Friedman, and Parker, 1973). Though the mean intelligence quotient of these patients treated early tends to lie about 10 points below that of the normal population, they are educable at normal schools and differ strikingly from most untreated or late-treated phenylketonuric children whose mean intelligence is about 50. Levy, Karolkewicz, Houghton, and MacCready (1970) ascertained the prevalence of PKU amongst a quarter of a million teenagers and adults who were being tested for syphilis. Only three subjects were found to have the condition and they were all mentally subnormal at least to a mild degree, so untreated subjects with phenylketonuria and of normal intelligence are not prevalent in the population.

In classical phenylketonuria the absence of liver phenylalanine p-hydroxylase results in a high level of phenylalanine in the blood and excretion of abnormal aromatic acid metabolites in the urine. By the middle of 1962 most infants born in England and Wales were being screened for phenylketonuria, (Medical Research Council Conference on Phenylketonuria, 1963), the majority by the Phenistix test on urine. It was later shown that this test, which involves the detection of phenylpyruvic acid in the urine, passes as normal perhaps a quarter or even a half of all children with the disease (eg, Stephenson and McBean, 1967). After looking at a number of tests, the Medical Research Council Working Party on Phenylketonuria in 1968 considered that a screening test which detected raised levels of phenylala-

nine in blood would be more satisfactory, and recommended the Guthrie test as particularly applicable. As a result of this report the Department of Health and Social Security recommended in HM(69) 72 that Phenistix testing of infants should be replaced by the Guthrie test on blood (Guthrie, 1961; Guthrie and Susi, 1963). Some areas use other methods for detecting raised phenylalanine in blood and these are equally satisfactory. This policy has produced most encouraging results as shown in tables I and II which are based on data obtained from the MRC/DHSS Phenylketonuria Register (Hudson and Hawcroft, 1973). It has also raised many problems, since infants with phenylalanine levels lower than those seen in classical PKU are detected by the screening procedure. Although figures for the birth frequency of classical PKU are quoted in the literature (eg, for the UK see Carter, 1973), they should be interpreted with caution in view of the increasing realization of the genetic heterogeneity of the condition. It may be only after several months of treatment that it becomes apparent that an infant is not behaving like a classical case of phenylketonuria. The system for the conversion of phenylalanine to tyrosine is a complex one involving a pteridine cofactor and dihydropteridine reductase in addition to the phenylalanine p-hydroxylase. In addition, tyrosine: alpha-ketoglutarate and phenylalanine: pyruvate aminotransferases and aromatic alpha-ketoacid reductase are involved in the conversion of phenylalanine to tyrosine (McLean, Marwick, and Clayton, 1973). Unfortunately these enzymes

occur only in liver and this has inhibited their study in atypical phenylketonuria and hyperphenylalaninaemia.

The detection of phenylketonuria by the Guthrie test is economically attractive. To screen each infant in north London for raised phenylalanine, raised methionine (to detect homocystinuria), and raised histidine (to detect histidinaemia) a research project costs 6.9p; this covers staff and materials in the laboratory. The cost of detecting an infant with phenylketonuria is thus about £700. In view of the fact that patients with untreated phenylketonuria are generally of such low intelligence that they ultimately require institutional care for many years, the screening service is of economic benefit to the community. A successful screening programme may shift the need for resources and finance from one part of the National Health Service to another. For example, with the larger numbers of early diagnosed infants with phenylketonuria, there is a steadily increasing workload for the paediatrician, dietitian, biochemist, and psychiatrist. On the other hand, the number of late detected patients presenting with mental retardation has fallen in a most gratifying way and the need for institutional care for patients with phenylketonuria as they reach their teens is steadily becoming less.

#### Screening for Histidinaemia

There are inherited conditions with definite biochemical abnormalities, the clinical significance of

Year of Birth	Under 4 Months	4-12 Months	Over 1 Year	Total
1964	22	3	10	35
1965	23	4	10	37
1966	29	4	6	39
1967	35	4	7	46
1968	35	1	5	41
1969	42	1	5	48
1970	56	2	—	58
1971	58	—	—	58
1972	40	—	—	40
Total	340	19	43	402

Table I Age when the diagnosis of phenylketonuria was confirmed in the UK<sup>1</sup>

<sup>1</sup>From Hudson and Hawcroft (1973)

Reason Tested	1964	1965	1966	1967	1968	1969	1970	1971	1972	Total
Routine screening	13	15	25	30	30	35	54	55	36	293
Sibling with phenylketonuria	9	10	5	8	6	9	2	3	4	56
Symptoms	12	10	7	8	5	4	2	0	0	48
Other	0	1	1	0	0	0	0	0	0	2
Not known	1	1	1	0	0	0	0	0	0	3
Total	35	37	39	46	41	48	58	56	40	402

Table II Reason for the diagnosis of phenylketonuria in the UK<sup>1</sup>

<sup>1</sup>From Hudson and Hawcroft (1973)

which is not understood, and histidinaemia (Ghadimi, Partington, and Hunter, 1961) is a good example. Biochemical findings include increased histidine in plasma and urine, raised urinary excretion of metabolites of histidine, marked reduction in histidine ammonia lyase (histidase) activity and urocanic acid content in the skin, and an abnormal histidine tolerance curve. The biochemical changes have usually been discovered during the investigation of a mentally retarded patient (eg, Wadman, van Sprang, van Stekelenburg, and de Bree, 1967; Gatfield, Knights, Devereux, and Pozsonyi, 1969) and this has led to studies on other members of the family whether retarded or not. Even with this bias to selection, Neville, Bentovim, Clayton, and Shepherd in 1972 found that amongst their own subjects and those in the literature, 28 of 42 with the typical biochemical findings had intelligence within the normal range (IQ > 80). Although seven had defective speech, Neville *et al* (1972) agreed with others (Gordon, 1970; Lott, Wheelden, and Levy, 1970) that the evidence does not support the view that there is a specific speech defect in histidinaemia. Neville, Bentovim, Clayton, and Shepherd (1972) also had reservations about the minor psychological abnormalities which some workers have reported in apparently normal histidinaemic subjects (Gatfield *et al*, 1969; Bruckman, Berry, and Dasenbrock, 1970). In their study Neville *et al* (1972) could find no biochemical difference between retarded subjects and those of normal intelligence and their frequent coexistence in one family would be against a genetic explanation. It is possible to lower the plasma histidine concentration by means of a low-histidine diet, and Neville *et al* (1972) obtained adequate biochemical control in three retarded patients aged 3, 12, and 5 years. No dramatic clinical changes were observed though the youngest showed some improvement initially.

When the 'biochemical histidinaemia' is detected during the screening of newborns a complex ethical problem arises. Should the infant be treated? First, the relationship of the biochemical findings to retardation is unknown. Secondly, if dietary treatment is given then it appears that, at best, in more than half the infants, it would be given unnecessarily. If the treatment were harmless, then the problem would be simplified but in fact the diet is potentially dangerous. It is likely to cause severe psychological strains in the child and his family and in any case it may not be optimum for brain growth. Even with the best care, it is known that an early treated patient with phenylketonuria will not be quite as intelligent as his normal siblings. It is not known whether this is due to his disease, to some defect in the diet, or to other factors. If a synthetic diet is

used unnecessarily it may mean that the child does not develop his full intellectual capacity. Neville *et al* (1972) concluded from their study that there was little justification for the use of a diet in infancy and they suggested that careful follow up of neonates detected by screening would help to solve this difficult problem. Neville, Clayton, and Lilly began to screen for histidinaemia by the Guthrie test in June 1971 (unpublished observations). So far they have detected 19 infants with persistent raised concentrations of histidine in plasma and abnormal metabolites in urine. This is an incidence of about 1 in 11 000 births. Their present age range is from 2 months to 2 years and 9 months, with 15 of them now being over 1 year. They have been seen approximately every six months and at this present preliminary stage no major developmental problems have arisen. There is certainly no justification for screening for this disorder on a national basis. It is a good example of a condition where a careful research study with emphasis on the natural history of the condition is fully justified.

#### Screening for Galactosaemia

Galactosaemia is an excellent example of an inherited condition for which treatment is available (Nadler, Inoye, and Hsia, 1969; Komrower and Lee, 1970) but screening for it presents some problems. Classically the condition has usually presented after the introduction of milk feeds, as failure to thrive with vomiting and diarrhoea and the development of impaired liver function with jaundice. Cataracts may occur within a few days of birth and mental development is retarded. Classical galactosaemia would be diagnosed in such patients by the demonstration of a deficiency of galactose-1-phosphate uridyl transferase in the red cells.

A new genetic abnormality resulting in a deficiency of uridyl transferase was described by Beutler, Baluda, Sturgeon, and Day in 1965, and they called this the Duarte variant. Subsequently, and particularly as a result of screening programmes, it has become apparent that there are several genetic forms of galactosaemia and that phenotyping is essential as a follow up of infants giving positive tests. Thus Kelly, Katz, Burns, and Boylan (1970) tested 141 402 infants in New York State and identified seven with persistent transferase deficiency. Of these, three were homozygotes, one was probably a homozygote, and three were heterozygotes. Similarly, Kelly, Desjardins, Armerdirg, and Burns (1973) demonstrated five forms of the condition, particularly using serial assays of uridyl transferase and studies of isoenzyme patterns.

There are two tests which have been used exten-

sively in screening for galactosaemia: a microbiological assay (Guthrie, 1968) and a fluorescence test (Beutler and Baluda, 1966). The striking finding to emerge from screening programmes is the fact that galactosaemia can in fact be an acute fulminating fatal disease with a particular susceptibility to *E. coli* infection (Shih, Levy, Karolkewicz, Houghton, Efron, Isselbacher, Beutler, and MacCready, 1971; Scheibenreiter and Thalhammer, 1972). Even though Shih *et al* (1971) collected the blood samples at 3 to 5 days of age and Scheibenreiter and Thalhammer (1972) at the fifth or sixth day of life, affected infants died before the diagnosis from the screening programme was available. It would therefore appear that screening, if done at all, needs to be on cord blood and reporting of results would have to be rapid. Alternatively, Komrower (1973) has suggested that screening should be confined to all sick newborns and newborn members of families at risk.

### Screening for Cystic Fibrosis

Cystic fibrosis is the commonest inherited disorder in our population, affecting 1 in every 2000 to 2500 births. Although over the years there has been improvement in the morbidity and mortality of this condition (Lawson, 1972, Mearns, 1972), it is difficult to assess how much of this is due to earlier diagnosis and treatment and how much is the result of general improvements in living standards (Brimblecombe and Chamberlain, 1973). For a number of centres in the USA, Warwick and Pogue (1969) found that only 25% of such children were alive at the age of 20 years. The sweat test (McKendrick, 1962) is the most helpful laboratory test for enabling the clinician to diagnose cystic fibrosis, but it is quite unsuitable as a screening test. An added difficulty is that young infants frequently do not sweat sufficiently in response to pilocarpine administered by iontophoresis and in any case it is an investigation which is often performed very badly (Gibson, 1973). It is essential to obtain a free flow of sweat and it is not advisable to report on samples smaller than 100 mg.

Various tests for screening for cystic fibrosis have been suggested, including the direct reading of the sodium content of unstimulated saliva with a sodium-sensitive electrode, determination of skin chloride with a direct-reading electrode, measurement of the conductivity of sweat and measurement of the sodium content of nails by neutron activation; all of them present problems in the first few weeks of life (Brimblecombe and Chamberlain, 1973).

A more hopeful approach to screening is based on the detection of protein in the meconium of the infant with cystic fibrosis. Green, Clarke, and

Schwachman (1958) reported that large amounts of serum protein, particularly albumin, were present in meconiums from patients with cystic fibrosis and since then pilot studies have shown that this is a practical method of screening (eg, Green and Schwachman, 1968; Cain, Deall, and Noble, 1972). Although further experience of this technique in pilot schemes is necessary, screening of the whole infant population for cystic fibrosis is not indicated at present, since this is a disorder with such a severe prognosis. The support of parents and patients by clinicians even in pilot surveys will be a major undertaking, and far more experience on how to handle the situation is required. So far, the basic defect in this disease has not been elucidated, nor is prenatal diagnosis yet a possibility. Unfortunately too, the separation of heterozygotes from homozygotes in population studies is not sufficiently precise to be of practical value (Conover, Bonforte, Hathaway, Paciuc, Conod, Hirschhorn, and Kopel, 1973).

### Screening for Tay-Sachs Disease

In an important project Kaback, Zeiger, Reynolds, and Sonneborn (1974) have studied a further aspect of population screening. Using a semi-automated method for hexosaminidase A in serum, backed up by determinations on white blood cells in selected individuals, they have detected carriers of Tay-Sachs disease. This prospective study was made in the Jewish communities of Baltimore, Maryland, and suburban Washington DC, and in the first year more than 300 carriers were detected amongst over 7000 individuals who volunteered to be tested. Eleven couples, both partners being carriers, were identified none of whom had previously had an affected child. This would enable all the pregnancies of such couples to be monitored for Tay-Sachs disease, and not just pregnancies occurring in families after an affected child had been born previously (O'Brien, Okada, Fillerup, Veath, Adornato, Brenner, and Leroy, 1971). Much information gained in this study will be of value when screening for heterozygotes is extended to other diseases. In particular, young married couples with future plans for children were enthusiastic. It must be remembered however, that not all populations are as health conscious as those in the USA! It does seem likely, however, that heterozygote detection and prenatal screening will play an increasingly important part in the care of individuals and communities.

### Conclusions

The disorders discussed in this paper demonstrate



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some of the advantages and undoubtedly difficult problems which screening presents. It is essential that no one should lose sight of the fact that the aim of screening is to help the individual and the community. The psychological aspects of screening are very important and continuing thought must be given to the fact that biochemical abnormalities do not necessarily equate with disease.

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