J. Roy. Coll. Phycns Vol. 10 No. 2 January 1976

The Value of Screening in Paediatrics

R. A. CARTER, MB, MRCP, FRCPath

Pathologist, Hollymoor and East Birmingham Hospitals

Screening means many different things to different people, but the definitions and criteria have been clearly set out in a recent review of this topic (Whitby, 1974) the concluding paper of which (Holland, 1974) set out criteria of value. In this article I would emphasise two definitions: *population screening* is the carrying out of some test or procedure on every individual within a population defined by such limits as geography, administration, race, sex or age; *at risk screening* is the carrying out of such a test or procedure on a person or persons for whom there already exists some medical reason to suppose that the findings may be positive. Some examples seem to fall between these two definitions, particularly in cytological screening for cancer, but in paediatrics the distinction is usually clear cut.

In the U.K. most paediatric population screening occurs either in the neonatal period or when the child first comes under the care of the School Health Service. At risk screening may occur at any time that an indication arises, but is most often pre-natal or in the first few weeks of life.

At risk screening is really only an extension of the normal doctor-patient relationship and of accepted medical care. If there is known to be a relative with Wilson's disease, it can only be good medical practice to test for this condition in the children of that family. Whitby (1974) opined that most screening procedures held to be worthwhile would fall in this category. Certainly it is easier to evaluate such techniques, as this can be done simply in terms of effectiveness. Does the screen identify the abnormal subject? If so, can anything useful be done about it? (Raine, 1969).

POPULATION SCREENING

The value of population screening, especially in the neonatal period, is a much more complex question. It involves something outside the normal doctor-patient relationship. It is really an administrative process, in which machinery is set up to deal with the population through a new channel. It is also part of community medicine.

In evaluating such screening procedures I would suggest that the following headings be considered. These are not claimed as the only possible, nor as ideal, but they simply serve as a guide.

1. Frequency of the condition sought.
2. Prospects for treatment or prevention of disability.

3. Practicability of the technique(s).
4. Cost benefit analysis, summing the above in monetary terms.
5. Social benefit (or cost) and eugenic potential.
6. Compassion and emotional pressure.
7. Contribution to scientific knowledge.

Armed with these criteria I would now like to examine some of the conditions proposed for or included in population screening programmes.

Congenital Dislocation of the Hip (CDH)

The incidence of the condition is around 1 per 1,000 of the population (Holt, 1974), treatment yields reasonably good results and the investigation itself requires no special equipment. The problems are that it does require skill and experience, and that some infants develop stable hips after only short periods in abduction. Hence, there may be both false negatives and positives. However, this is a generally accepted screening technique, which is almost certainly cost effective, and is historically one of the earliest. Because it relies wholly on clinical as opposed to laboratory expertise it is not always thought of in terms of screening.

Phenylketonuria (PKU)

This is the classic example of a total population screen. Following the report of the M.R.C. Working Party (1968) the Department of Health instituted a national policy for such screening. Either microbiological methods (Guthrie and Whitney, 1965), chromatographic techniques (Scriver *et al.*, 1964) or automated fluorimetry (Holton, 1972) are now used and the success of this policy has been reviewed by Hawcroft and Hudson (1974).

It may be seen that PKU satisfies the criteria given above. The incidence (ranging from 1 : 6,000 in Western Scotland to 1 : 20,000 in South East England) is a little low, and large throughput is needed to maintain experience of positive findings. Amenability to treatment is now well established (Seakins *et al.*, 1973; Raine, 1975) and the tragic natural outcome of the disorder meets the criterion of compassion. A cost benefit analysis is set out in Table 1.

These figures involve many assumptions and are only a guide to the order of magnitude involved. They do show how one may tackle this problem, and emphasise the way that small differences in cost per test will multiply up to represent thousands of pounds.

Holland (1974) has gone so far as to suggest that PKU is the only population screen to meet criteria of validity at the present time; the value of other screens is much less clear cut.

Galactosaemia

Here the incidence is much lower, 1 : 40,000 or less (Raine, 1974), and the majority of these babies will be seriously ill by the sixth day when PKU testing is

Table 1. Phenylketonuria detection: cost-benefit analysis: 1974 prices.

Cost of West Midlands PKU Laboratory Service	
(Staff, materials, clerical, postage and depreciation of major items) .	£4,500 per annum
Cost of Area Health Authority Organisation and Collection	
(Postage, collection time, mileage, record keeping and correspondence)	£15,000 per annum
Number of Cases Found	3.2 per annum
Cost of Finding One Case	£6,000
Cost of Diet, given for 10 Years	£30,000
(Many now give it for less: Seakins *et al.*, 1973)	
Medical Care and Follow Up	£1,000
Total Cost:	£37,000
Less contribution made during life both by working in the community and by paying taxes	Not Quantified
Cost of Not Diagnosing a Case:	
Average inpatient cost of a West Midlands subnormality hospital is £30 per week	
For say 30 years this means	£46,800
There is also unlikely to be any deduction for contribution to society.	

done. Thus, the use of the samples taken in the national PKU programme could serve to detect only mild, atypical or missed cases. Treatment is highly effective and less difficult than PKU, but to be useful screening would have to be on blood taken on the first day. It would also be necessary to ensure rapid transport of specimens and prompt reporting of positive findings. A Guthrie type screening method is practicable, though less robust than the PKU technique and is in use in some centres in the U.K. (Lindsay, 1972). Biochemical screening techniques also exist (W.H.O., 1968).

Maple Syrup Urine Disease

This presents a similar dilemma (W.H.O., 1968), but the incidence is even lower and treatment is much more difficult (Seakins *et al.*, 1973; Raine, 1975). Guthrie techniques are again available, and amino acid chromatography detects the condition with ease.

Homocystinuria

This condition may be detected either by Scriver or Guthrie techniques, and, because it is slowly progressive, the routine PKU sample is usable. The incidence is low (no exact figures are available as yet), but there is progressive clinical disability, with lens dislocation, mental retardation, fits, laxity of connective

tissue and a thrombotic tendency. Treatment of some cases is relatively inexpensive as these respond to pyridoxine, but those who can be controlled only by methionine restriction are difficult and costly to treat. Treatment must be continued for much longer than with PKU (Raine, 1975). Clearly, for the pyridoxine responsive cases this is a promising addition to the PKU screen. Unfortunately, the rarity of the condition and the quite frequent occurrence of raised methionine levels from other causes detract from the cost effectiveness.

Other Aminoacidopathies

These include histidinaemia, prolinaemia and Hartnup disease. Centres using plasma amino acid chromatography (Raine, 1972b; Scriver *et al.*, 1964) will detect these and others as part of their routine PKU service so that no extra cost is involved up to the point of diagnosis. Guthrie centres can also detect some of these, but the techniques are additional and sometimes difficult (Lindsay, 1972).

Table 2 shows the commoner possibilities.

Table 2. Tests possible using the two most general PKU screening techniques.

Guthrie	Scriver
Phenylketonuria	Phenylketonuria
Histidinaemia	Histidinaemia
Tyrosinaemia	Tyrosinaemia
Homocystinuria	Homocystinuria
Maple syrup urine disease	Maple syrup urine disease
Galactosaemia	Prolinaemia
	Hartnup disease
Discs also usable for G-6. P.D. deficiency testing, and possibly abnormal haemoglobins	Cystinuria
	Aminoglycinuria
	Plasma: hyperlipidaemia
	Red cells: haemoglobins, and G-6. P.D. deficiency

The incidence of most of these conditions is appreciably lower than that of PKU and the need for treatment is often ill defined (Raine, 1972a; Seakins *et al.*, 1973; Raine, 1975). At present we lack experience and supporting facilities for the management of such conditions in much of the U.K. Also we do not really have enough knowledge of many of them to apply the criteria previously mentioned. Were it not that diagnosis was a by-product of the Scriver technique for PKU it is doubtful if they would be searched for.

Glucose 6 Phosphate Dehydrogenase Deficiency in Red Cells (G-6.P.D. Deficiency)

This is an example of another type of problem—the search for a genetic defect that does not immediately cause disease, but may place the individual in danger at

a later date when some specific challenge occurs. It is quite practicable to screen for this disorder using an automated fluorimetric technique (Dickson *et al.*, 1973) or by a simple enzyme reaction with visual assessment under ultraviolet light (Dow *et al.*, 1974). Neither method is very costly and both are compatible with existing programmes. The incidence in Negroes (12 per cent; Uddin *et al.*, 1974) makes it an attractive proposition in areas with high immigrant populations like the West Midlands Metropolitan County. However, there are substantial problems in conveying the knowledge to the patients' families and their medical attendants and explaining the significance of the finding. Adequate personal records systems might in time overcome these.

Similar considerations apply to screening for pseudocholinesterase variants (Scoline apnoea), porphyria and abnormal haemoglobins. Some of these are certainly justified as at risk screens in selected populations (W.H.O., 1968) but at present none seems suitable for mass screening, both because of technical complexity, and low incidence in the general populace. Recently, a technique for the detection of abnormal haemoglobins has been described and claimed to be suitable for population screening (Thambipillai and Senewiratne, 1975). This uses filter paper samples such as are submitted for Guthrie PKU screening. Such technical advances may from time to time alter the practicability and cost effectiveness of any particular screening project.

Now I would like to turn to two relative newcomers to this field.

α-1 Antitrysin Deficiency

It is now established that there is an association between homozygous deficiency of this factor and both pulmonary emphysema and juvenile cirrhosis, and that heterozygotes also show an increased risk of developing these disorders (Sun *et al.*, 1974). The heterozygote incidence is between 5 per cent and 14 per cent and screening techniques capable of detecting heterozygotes exist, but are rather expensive and time-consuming. Of these, radial immunodiffusion seems the most promising, although enzyme activity may also be measured (Sun *et al.*, 1974; Endre and Boda, 1974). The hope is that those found to be heterozygous can benefit from the knowledge by avoiding smoking, pollution and dusty employment, as these all predispose such persons to develop overt disease (Mittman *et al.*, 1971; *British Medical Journal*, 1974).

α-Fetoprotein

When there is an open defect of the neural tube of the developing fetus (spina bifida or anencephaly) the amniotic fluid contains a raised level of this protein (Brock and Sutcliffe, 1972). More recently it has been recognised that this may be reflected in the maternal serum (Brock *et al.*, 1973; Leek *et al.*, 1973; Seller *et al.*, 1974). Despite some doubts about the reliability of this test (Laurence, 1974; Harris *et al.*, 1974; Wald *et al.*, 1974) it has been proposed that all pregnant women should be screened in this way with a view to therapeutic termination of

pregnancy if its presence is confirmed (Leek *et al.*, 1974; Leek and Chard, 1974). The most reliable technique appears to be radioimmunoassay, but the whole basis of this particular screen is at present controversial.

Next I wish to turn to two old established disorders for which new screening prospects have recently emerged—

Congenital Hypothyroidism

Levels of thyroxine and triiodothyronine show considerable variation in the first few days of life and are influenced by maternal oestrogens, so making them rather unsuitable as indicators of thyroid dysfunction (Abuid *et al.*, 1974; Similä *et al.*, 1975). Also, techniques for measurement are rather unsuitable for the numbers involved. More recently it has been found that thyroid stimulating hormone (TSH) is a reliable guide to hypothyroidism both in cord blood and after 3 to 4 days of neonatal life (Klein *et al.*, 1974; Similä *et al.*, 1975; Barnes, 1975). Immediately after birth the serum TSH begins to rise, and by two hours is well above normal adult levels. It returns to the adult normal range by 48 hours (Similä *et al.*, 1975). The value of early diagnosis is already accepted and the incidence of around 1 : 8,000 makes this screen seem promising (Klein *et al.*, 1971; Dacou-Voutetakis, 1971). Can TSH assay be made available for mass screening? This is largely a question of technique and enterprise by those who raise the antisera, although supplies of human TSH for standardisation may prove to be a limiting factor. Techniques for the automation of large numbers of radioimmune assays are now available. A pilot trial is needed to determine the reliability, practicability and cost effectiveness of this screen, and, as with so many of these problems, will need to be on a fairly large scale to secure adequate cases.

Cystic Fibrosis (Mucoviscidosis)

This disorder has a high incidence (1 : 2,000; Raine, 1974) and may be heterogeneous. Many screening techniques have been tried and found wanting in either reliability or practicality. The recent finding of increased levels of serum proteins in the meconium (Ryley *et al.*, 1974) has reawakened interest in this field, but already there are reports of both false positives and negatives (Stephan *et al.*, 1975; Raine, 1974). A simple stick test similar to those used for clinical urine testing has been made commercially available, and is being used by individual maternity hospitals. This results in any one unit detecting so few cases only that it will be a long time before the true utility of such a method becomes clear. Despite problems over loss of protein in the post (Stephan *et al.*, 1975) it might be preferable to submit specimens to a central laboratory where more sensitive and reliable techniques can be applied. The hope here is that early diagnosis and consequent early sustained antibiotic therapy will minimise lung damage from recurrent infections, while suitable diet and replacement therapy can minimise the effects of pancreatic dysfunction. In this way improved survival and a better quality of life may be obtained (*British Medical Journal*, 1971; Deall, 1971).

CONCLUSION

This review of conditions for which population screening may be considered is not exhaustive, but it serves to show the central dilemma in this field, which is that, apart from CDH, PKU and possibly homocystinuria, none seems to show quite strong enough a case to be considered worthwhile screening for on its own. The reasons for this vary from one condition to the next (e.g. incidence, technical difficulty in testing, absence of effective therapy) and technical advances are likely to change the validity of some of these reasons with time. What then is the likely pattern of development of screening in the U.K.?

1. To continue as at present, with most of the country covered for CDH and PKU; about one-fifth will also be covered for the disorders detected by the Scriver technique or extra Guthrie tests. Without any official help or guidance this seems likely to be the course for the next few years at least.
2. To add to the present techniques piecemeal, as and when local enthusiasm, technical advances and finance permit. Again this reflects present practice, but leads to very uneven standards over the country as a whole.
3. That we develop and, when finances permit, implement a new national policy. What I would like to see happen is—

   (*a*) That we accept double screening for every infant, i.e. cord blood and a 6 to 9 day sample.

   (*b*) That we establish well-staffed and equipped laboratories at regional or supra-regional level to receive these specimens.

   (*c*) That these test for as many conditions as practicable (including nearly all of those mentioned above). The rationale of this is that once the specimens are collected and once laboratory staff and equipment are assembled, it costs much less to do a whole series of tests than it would to do them individually. Also, there will be sufficient positive findings to sustain interest, and to make the whole venture worthwhile.

   (*d*) That the laboratories have a close association with clinical staff who can follow up the patients and advise on treatment or management. They will also need facilities for confirmatory tests and for more detailed characterisation of the defects in those with positive findings.

   (*e*) That the laboratories should have a good records system, in which any child's findings can be looked up with reasonable ease, at least until they are established at school. This system would also produce warning cards for conditions like G-6.P.D. deficiency and porphyria. It would probably need to be based on some form of electronic data processing.

In effect, the sum of a comprehensive screening service, well planned and executed, would greatly exceed that of its component parts in usefulness, while being much less than them in total cost.

This article is based on a paper read at the College conference 'Achievements and

illusions—the value of some current practices', held in Coventry in September 1975.

References

Abuid, J., Klein, A. H., Foley, T. P. and Larsen, P. R. (1974) *Journal of Clinical Endocrinology and Metabolism,* **39**, 263.

Barnes, N. D. (1975) *Archives of Disease in Childhood,* **50**, 497.

British Medical Journal (1971) **3**, 489.

British Medical Journal (1974) **1**, 527.

Brock, D. J. H., Bolton, A. E. and Monaghan, J. M. (1973) *Lancet,* **2**, 923.

Brock, D. J. H. and Sutcliffe, R. G. (1972) *Lancet,* **2**, 197.

Dacou-Voutetakis, C. (1973) *Archives of Disease in Childhood,* **48**, 826.

Deall, A. M. (1971) *British Medical Journal,* **3**, 639.

Dickson, L. G., Johnson, C. B. and Johnson, D. R. (1973) *Clinical Chemistry,* **19**, 301.

Dow, P. A., Petteway, B. A. and Alperin, J. B. (1974) *American Journal of Clinical Pathology,* **61**, 333.

Endre, L. and Boda, D. (1974) *Lancet,* **1**, 631.

Guthrie, R. and Whitney, S. (1965) United States Department of Health, Education and Welfare, Children's Bureau Publication 419-1964, Revised 1965. Washington.

Harris, R., Jennison, R. F., Barson, A. J., Laurence, K. M., Ruoslahti, E. and Seppälä, M. (1974) *Lancet,* **1**, 429.

Hawcroft, J. and Hudson, F. P. (1974) *Health Trends,* **6**, 72.

Holland, W. W. (1974) *Lancet,* **2**, 1494.

Holt, K. S. (1974) *Lancet,* **2**, 1057.

Holton, J. B. (1972) *Annals of Clinical Biochemistry,* **9**, 118.

Klein, A. H., Agustin, A. V. and Foley, T. P. (1974) *Lancet,* **2**, 77.

Klein, A., Meltzer, S. and Kenny, F. (1971) *Pediatric Research,* **5**, 399.

Laurence, K. M. (1974) *Lancet,* **2**, 939.

Leek A. E. and Chard, T. (1974) *Lancet,* **1**, 876.

Leek, A. E., Leighton, P. C., Kitau, M. J. and Chard, T. (1974) *Lancet,* **2**, 1511.

Leek, A. E., Ruoss, C. F., Kitau, M. J. and Chard, T. (1973) *Lancet,* **2**, 385.

Lindsay, G. (1972) *Annals of Clinical Biochemistry,* **9**, 115.

Medical Research Council Working Party on Phenylketonuria (1968) *British Medical Journal* **4**, 7.

Mittman, C., Lieberman, J., Marasso, F. and Miranda, A. (1971) *Chest,* **60**, 214.

Raine, D. N. (1969) *Annals of Clinical Biochemistry,* **6**, 29.

Raine, D. N. (1972a) *British Medical Journal,* **2**, 329.

Raine, D. N. (1972b) *British Medical Journal,* **3**, 7.

Raine, D. N. (1974) *Lancet,* **2**, 996.

Raine, D. N. (1975) *The Treatment of Inherited Metabolic Disease.* Lancaster: Medical and Technical Publishing.

Ryley, H. C., Neale, L., Brogan, T. D. and Bray, P. T. (1974) *Archives of Disease in Childhood,* **49**, 901.

Scriver, C. R., Davies, E. and Cullen, A. M. (1964) *Lancet,* **2**, 230.

Seakins, J. W. T., Saunders, R. A. and Toothill, C. (1973) *Treatment of Inborn Errors of Metabolism.* London: Churchill Livingstone.

Seller, M. J., Singer, J. D., Coltart, T. M. and Campbell, S. (1974) *Lancet,* **1**, 428.

Similä, S., Koivisto, M., Ranta, T., Leppäluoto, J., Reinilä, M. and Haapalahti, J. (1975) *Archives of Disease in Childhood,* **50**, 565.

Stephan, U., Bräuning, C. and Busch, E. W. (1975) *Lancet,* **1**, 167.

Sun, T., Kurtz, S. and Copeland, B. E. (1974) *American Journal of Clinical Pathology,* **62**, 725.

Thambipillai, S. and Senewiratne, B. (1975) *American Journal of Clinical Pathology,* **63**, 836.

Uddin, D. E., Dickson, L. G. and Brodine, C. E. (1974) *Journal of the American Medical Association,* **227**, 1408.

Wald, N. J. Brock, D. J. H. and Bonnar, J. (1974) *Lancet,* **1**, 765.

Whitby, L. G. (1974) *Lancet,* **2**, 819.

World Health Organisation (1968) *Screening for Inborn Errors of Metabolism.* Report of a W.H.O. Scientific Group. W.H.O. Technical Report Series No. 401. Geneva.