Prevention of Hereditary Disease*

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SUMMARY

A number of hereditary diseases are amenable to treatment by manipulation of the environment, and the results of this approach are encouraging. Some of these conditions need to be diagnosed soon after birth if serious effects are to be prevented. Neonatal screening programmes are therefore indicated. Other hereditary diseases either defy treatment completely or else have an extremely bad prognosis even when the best treatment is provided. Recent advances in the field of prenatal diagnosis of hereditary disorders have made it possible to 'prevent' the birth of children with a number of these conditions.

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Hereditary diseases are assuming greater relative importance in the practice of medicine. In the developed countries 25 - 30% of admissions to paediatric hospitals are for diseases due, wholly or in part, to genetic causes.

In our country we are confronted with problems of malnutrition and infectious disease of such magnitude that it might be considered a 'luxury' or a complete lack of sense of priority to concern oneself with hereditary disease. Nevertheless, we do have sections of our population (not confined to the Whites) in which malnutrition and infectious diseases are no longer serious problems. These 'sophisticated' South Africans are increasing in number annually. It is reasonable to expect that if people respond to appeals to restrict the size of their families they must be helped to ensure that the children they do produce will be healthy—in body and mind.

Until about 3 years ago the medical geneticist could help diagnose hereditary diseases and treat a few of them; but, for all practical purposes, his main function was the giving of probability figures relating to the risks of recurrence. Then some major break-throughs were made which enabled certain genetic diseases (both chromosomal and biochemical) to be diagnosed when the fetus was sufficiently small to permit consideration of termination of pregnancy. Commensurate with these advances in antenatal diagnosis came changes in society's attitude to abortion.

The physician, dealing with families in which there was a high risk of genetic disease, was no longer a relatively helpless bystander but became an important *dramatis personae*, capable of 'preventing' the birth of children with severe crippling, incapacitating diseases, many of which are fatal within a few years of birth.

In September 1973 I attended the Fourth International Conference on Birth Defects held in Vienna.

The National Foundation—March of Dimes, sponsors of this Conference, is a remarkable voluntary health organisation. Founded in 1938 by President Roosevelt to fight poliomyelitis it had, within 20 years, helped conquer the disease. In 1958 the Foundation turned its attention to birth defects. A broad definition of the term birth defects was adopted: 'Those human conditions, significantly handicapping to their bearers, that are of prenatal origin due to genetic, environmental, or combined genetic-environmental causes, and manifest at birth or various ages later in life'.

There was a strong multidisciplinary flavour to the Conference, with molecular biologists and other laboratory scientists interacting with obstetricians, paediatricians and human geneticists of different subspecialities. There were teratologists, epidemiologists, virologists, social workers, veterinarians and pharmacologists. Two hundred and eighty-nine papers were read in 5 plenary sessions, at 9 workshops and at 14 sessions for free communications, many of which were held simultaneously.

This article concentrates on one general theme, namely the prevention of hereditary disease, related to problems in medical genetics as they present themselves in South Africa.

Replacing the abnormal gene with a normal gene would appear to be the ultimate in gene therapy and the exciting feats of synthesising DNA were reviewed by Dr Paul Marks of Columbia University, New York City, in whose laboratory attempts to introduce globin genes into animal cells *in vitro* have met with some success. Merril, from the National Institute of Health, Bethesda, Maryland, who claimed a year ago to have succeeded in introducing a gene from one cell into another by means of a virus (the prokaryotic galactose operon genes, carried by an *Escherichia coli* tranducing lambda phage, into human galactosaemic fibroblasts) presented new data which tended to confirm his earlier work.

But genetic engineering has not 'arrived'; it is still in the realm of science fiction. An alternative approach to the treatment of genetic disease is environmental engineering or manipulation by substrate restriction or metabolite (product) replacement, thereby bypassing the mutant gene product. Dr C. R. Scriver of McGill University Montreal Children's Hospital reviewed this field.

Table I sets out some of the hereditary diseases which are susceptible to treatment by dietary or pharmacological means. It will be seen that by substrate reduction, by cofactor supplementation, by metabolite or enzyme replacement, or by removal of toxic products many of the sequelae of these genetic diseases may be prevented.

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TABLE I. HEREDITARY (METABOLIC) DISEASES SUSCEPTIBLE TO TREATMENT (DIETARY OR PHARMACOLOGICAL)*

Disease	Mode of treatment
Disorders of amino acid metabolism	
Argininaemia	S,prot
Citrullinaemia	S,prot
(Cystinuria)	D-penicillamine
(Histidinaemia)	S,his
Homocystinuria	S,met; P,cyc; V
Hyperlysinaemia	S,prot
Phenylketonuria	S,phe
Disorders of carbohydrate metabolism	
Disaccharidase deficiency	S, lact, etc.
Galactosaemia	S,gal
Fructose intolerance	S,fructose
Disorders of lipid metabolism	
Hyperlipoproteinaemias (various types)	S, lipids; P, triglycerides (various combinations)
Refsum's disease	S,phytanic acid
Miscellaneous	
Hyperuricaemia(s)	Enz (artificial block)
Oroticaciduria	P,uridine
Wilson's disease	D-penicillamine, potassium sulphide
Hypophosphataemic states	P,phosphate
Hereditary hormone deficiencies (e.g. thyroid deficiency, adrenogenital syndrome, diabetes insipidus)	
Vitamin-responsive traits	
Megaloblastic anaemia	V,B_1
Pyridoxine dependency (convulsions)	V,B_6
Cystathioninuria (one form)	V,B_6
Methylmalonicaciduria (one form)	V,B_{12}
Vitamin B_{12} malabsorption	V,B_{12}
Pseudodeficiency rickets (vitamin D dependency)	V,D_2 or D_3

* Material adapted from Scriver,[2,3] and O'Brien and Goodman.[4] Abbreviations: S = substrate restriction; P = product replacement; Enz = enzyme replacement; V = vitamin supplementation; term following indicates component adjusted.

Another group of inherited disorders place the patient at an altered risk in particular environments (Table II). The environment in question is often that produced by the medical practitioner in his well-intentioned attempt to help the patient. Isoniazid in the usual dosage can cause polyneuritis due to a deficiency of a transacetylase enzyme which, when present, will conjugate the drug. We are at the moment engaged in a study to determine the prevalence of this trait in Southern Africa and can report that the Kalahari San ('Bushmen') have a much lower prevalence of the deficiency than all other groups so far tested.[6] Anaesthetists occasionally are made aware of the dangers of genetic traits like pseudo-cholinesterase variation when a patient fails to breathe for many hours after receiving a 'normal' dose of succinylcholine.

But the doctor cannot be blamed for all the catastrophes in this category—self-inflicted noxious agents like alcohol and tobacco smoke can, if the individual has a particular inherited trait, be responsible for alcoholism or pulmonary emphysema. In both of these categories individuals can be identified by mass screening procedures and steps taken to prevent the development of the disease by the appropriate means.

If treatment, in order to be successful, has to be instituted within a matter of days after birth, as with classical phenylketonuria (PKU), then neonatal screening is essential. I understand from Dr Sylvia Johnson of the Johannesburg City Health Department that her Department between 1964 and 1969 tested approximately 43 000 White, 5 000 Coloured and 750 Asian babies aged 2 - 3 weeks with the Phenistix test on urine without finding a single case of phenylketonuria. Holtzman of the Johns Hopkins Hospital, using the urine ferric chloride test, found that as many as 45% of PKU infants were initially negative. Since 1963, screening for blood phenylalanine elevations has been adopted and an evaluation of the success of the programme was attempted. It was found that 70% of newborns were screened before an elevated phenylalanine level could be expected to be detected. At least 22 infants (8% of infants with PKU screened) were missed by neonatal screening. Differences in interpretation and performance of the test were probably responsible for the differences in the incidence of PKU. Follow-up of suspected cases of PKU was poor, 24,9 days being the mean period taken for a repeat test to be carried out.

Neonatal screening programmes are beset by many problems. A number of countries have introduced them and the experience of the Quebec network is most encouraging. Using a fluorometric assay and a sample of blood submitted through the post on a piece of filter paper they claim good results screening for phenylketonuria, tyrosinaemia and galactosaemia. One-dimensional partition chromatography of amino acids in the urine of the newborn infant is also carried out—a separate sheet of filter paper being used for the collection. They are subsidised by the Government—$3 per birth, which covers the costs of these tests and supervision of the treatment of cases discovered. In addition, they have been able to add other investigations, like that for a Tay-Sachs disease carrier screening programme, at a marginal increase in cost.

The time has come to reconsider neonatal screening for inborn errors of metabolism in South Africa.

Other inherited metabolic defects need not be detected in the neonatal period for catastrophic results to be avoided. There is probably time enough to test a person for his acetylator status before putting him on isoniazid therapy; or his plasma pseudocholinesterase type before giving him an anaesthetic which includes succinylcholine (Scoline). But in certain populations it may be wise to screen all patients admitted to hospital so that the physician or anaesthetist is alerted to the dangers of administering certain drugs. Glucose-6-phosphate dehydrogenase defi-

TABLE II. SOME INHERITED DISORDERS PLACING THE PATIENT AT ALTERED RISK IN PARTICULAR ENVIRONMENTS*

Trait or system affected by the mutation	Environment or condition	Effect in patient at risk
'Specific' hydroxylase	Diphenylhydantoin	Dilantin toxicity
INH transacetylase	Isoniazid (sulphamethazine, hydralazine, phenelzine)	Polyneuritis
Glucuronide transferase. (Gilbert's disease; and Crigler-Najjar syndrome)	Salicylates, tetrahydrocortisone, menthol	Jaundice and drug toxicity
Porphyria variegata and hepatic type	Barbiturates	Increased porphyrin synthesis; acute 'attack'
Atypical alcohol dehydrogenase	Alcohol	Increased alcohol tolerance
Pseudo-cholinesterase	Succinylcholine	Apnoea
Glucose-6-phosphate dehydrogenase (some mutations)	Primaquine, sulphonamides, etc.	Haemolysis
Haemoglobin		
Haemoglobin S (heterozygote)	Hypoxia (e.g. with anaesthesia, altitude)	Intravascular sickling
Haemoglobin H	Sulphonamides, nitrates	Haemolysis
Haemoglobin Z	Sulphonamides, primaquine	Haemolysis
Methaemoglobins	Sulphonamides	Haemolysis and methaemoglobinaemia
Hereditary resistance to coumarin anticoagulants	Warfarin	↓ Response to warfarin ↑ Response to vitamin K
Phenylketonuria	Catecholamines	↑ Pressor response
Familial dysautonomia	Catecholamines	↑ Pressor response
Down's syndrome	Atropine	Sensitivity to drugs
α_1-antitrypsin	Smoking	Pulmonary emphysema

* Adapted from Clow *et al.*[5]

ciency would make the physician cautious when administering oxidant drugs like aspirin, phenacetin, sulphonamides or primaquine; in South Arica, as we are all aware, it would be dangerous to give barbiturates or sulphonamides to someone with porphyria variegata. In fact, 20 years ago Dr Geoffrey Dean screened all patients for this condition prior to their admission to hospital in Port Elizabeth—this might well have been something of a pioneering venture.

So far we have considered hereditary diseases amenable to treatment and the results are reasonably encouraging. Although we are not tackling the problem of prevention at the gene level, by controlling the environment individuals are helped to live fairly normal, useful lives.

There are unfortunately a number of hereditary diseases which either defy treatment completely or else have an extremely bad prognosis even when the best treatment is provided. It is for the 'prevention' of diseases such as these that antenatal diagnosis and selective abortion may be offered. In order to illustrate the way in which such programmes operate or could conceivably operate, a recessively inherited disease (Tay-Sachs disease), a chromosomal aberration (Down's syndrome, trisomy-21 or 'mongo'ism') and a multifactorially inherited disease (spina bifida/anecephaly) will be discussed.

TAY-SACHS DISEASE

Tay-Sachs disease, one of the lipidoses, is characterised by an accumulation of monosialoceramidetrihexoside (G_{M2}) in the neurones of the brain, owing to the absence of hexosaminidase A, which is essential for the initial step in the degradation of G_{M2}.

An affected child appears normal at birth but by 4 - 6 months is listless and hypotonic with steadily increasing retardation. The macula degenerates and 90% of cases show a cherry-red spot at the fovea. As cerebral degeneration proceeds the EEG becomes abnormal and epileptic seizures often occur before death supervenes between 2 and 4 years of age.

At autopsy the brain contains up to 100 times the normal amount of G_{M2} and the spleen and liver also contain detectable amounts of G_{M2}. Hexosaminidase A is not detectable in the serum or white cells.

The parents can be shown to be carriers of the gene for Tay-Sachs disease by possessing reduced levels of hexosaminidase A in serum and white cells. The disease is inherited as an autosomal recessive and the affected fetus can be diagnosed as early as 9 weeks' gestation. Amniocentesis at 14 - 16 weeks' gestation and assay of hexosaminidase A in the amniotic fluid, but preferably in cultured amniotic cells, can show conclusively if the fetus is suffering from the disease.

It has been known for over 70 years that Tay-Sachs disease is commoner in the Ashkenazi Jewish populations originating in certain regions of easten Europe than in other populations and it is likely that as many as 1 in 25 to 1 in 30 Ashkenazi living in the USA carry this defective gene. Preliminary data show that in South Africa there is a similar prevalence and a mass screening programme could be expected to reveal all carriers.

With the exception of the few recessively inherited diseases where prospective parents have been screened for the presence of the gene, parents are not usually aware that they are carriers of the recessive trait until a child with the disease has been born. It is apparent, therefore, that the birth of the first affected child cannot be

TABLE III. PREVENTION OF AUTOSOMAL RECESSIVE DISEASES: RETROSPECTIVE DIAGNOSIS AFTER BIRTH OF AFFECTED CHILD*

Pregnancy	Total number of fetuses	Number of normal children	Number of affected children	Number of intra-uterine diagnoses	Number of abortions of affected fetuses
1	480	360	120	—	—
2	360	270	90	—	—
3	120	90	—	120	30
	210	157	—	210	53
4	75	56	—	75	19
5	25	18	—	25	6
6	7,6	5,7	—	7,6	0,9
7	2,3	1,6	—	2,3	0,67
8	0,6	0,48	—	0,6	0,17
Total	1 280,5	959,78	210	440,5	109,74

* Corrected version of Motulsky *et al.*[7] 480 matings between heterozygote carriers; reproductive aim is normal children per couple.

prevented. But if intra-uterine diagnosis of the particular disease is possible the birth of subsequently affected children can be prevented.

Let us consider the quantitative problems involved in any programme designed to help such carrier couples have 2 normal children. To facilitate the calculations 480 matings are considered and the various steps are shown in Table III.

After the first pregnancy 360 couples will have 1 unaffected child each, while 120 will each have had an affected child and will have been alerted. The 360 couples will embark upon their second pregnancy unaware of their carrier status and 25%, i.e. 90 couples will produce an affected child. For them, and the 120 couples already alerted antenatal diagnosis with selective abortion is offered in future pregnancies. Thirty of the latter group (i.e. 25% of 120) will be found on antenatal testing to be carrying an affected fetus while 90 will be reassured. Embarking on a third pregnancy will be 210 couples—the other 270 having completed their families of 2 unaffected childern without ever knowing that they were carriers of the gene.

Intra-uterine diagnosis will have to be attempted in 210 couples — 53 will need an abortion and 157 will have been reassured that they have an unaffected child and will therefore have completed their families. The 75 unfortunates will have an amniocentesis during their fourth pregnancy — 56 will be reassured while 25 will have to embark on a fifth pregnancy. Fewer than 8 couples will need to undertake a sixth pregnancy and less than 1 couple out of the 480 will be unable to have fulfilled the aim of having 2 unaffected children after 8 pregnancies.

A total of 440 intra-uterine diagnostic procedures and 110 abortions would have been required for each of the 480 couples to have 2 normal children. But 210 affected children will also have been born and this is only 30 fewer than the affected number, assuming that the 480 couples had had 2 children each irrespective of the outcome of the pregnancy. The net reduction in affected children would be from 240 to 210 or only 12,5%.

But perhaps a fairer comparison would be between the number of affected children produced in monitored pregnancies as calculated above, and the number of affected children produced by 480 heterozygous parents if they were to reproduce until each couple had 2 normal children without monitoring of pregnancies subsequent to the birth of an affected child. Here the reduction is from 320 affected offspring to 210, or a 34% reduction.

Some words of caution need to be added at this point. Firstly, there are still relatively few genetic diseases in which the biochemical lesion has been sufficiently well characterised to permit of antenatal diagnosis. Secondly, many recessively inherited diseases are not diagnosed early enough to enable the rational approach of prenatal diagnosis to be planned prior to the second (or even the third) pregnancy.

Nevertheless, the type of programme outlined above could be instituted for a number of diseases with, under ideal conditions, the results predicted.

The detection of all heterozygotes prior to marriage and reproduction and the successful implementation of an antenatal diagnostic programme could, theoretically, result in the prevention of the birth of all children suffering from a recessively inherited disease. It is not at this stage practicable to screen everyone for a particular mutant gene but certain 'high-risk populations' (high frequencies of the gene) can be defined and these offered screening tests for detecting carriers.

The Ashkenazi Jewish population of South Africa with its high prevalence of Tay-Sachs disease would qualify for consideration as a high-risk population. Making a number of assumptions we have calculated that about 1 child with Tay-Sachs disease will be born to Ashkenazi parents in South Africa per year and that at any one time there will be about 4 such affected children in the country (Table IV). In order to prevent, by selective abortion, the birth of this child it is calculated that about 20 000 people will have to be tested initially, and perhaps

500 every subsequent year, while 4 amniocenteses per annum will have to be performed.

TABLE IV. TAY-SACHS DISEASE IN THE SOUTH AFRICAN ASHKENAZI JEWISH POPULATIONS: SOME THEORETICAL CONSIDERATIONS

Ashkenazi Jewish population	about 120 000
Approximate frequency of Tay-Sachs carrier state	1 in 30
Estimated number of couples of child-bearing age	19 500
Frequency of marriage between carriers (1 in 30)[2]	= 1 in 900
∴ estimated number of marriages between carriers $\frac{19\,500}{900}$	= 22
Assumed maximum mean number of children per sibship	4
Probability that a child of a carrier couple will have TSD	1 in 4
Assumed mean duration of child-bearing period	25 yrs
∴ annual mean No. of births of TSD children to the Ashkenazi community $\frac{1}{4} \times \frac{4}{1} \times \frac{22}{25}$	= 0,88
Maximum duration of life of a TSD sufferer	4,5 yrs
∴ maximum mean number of Ashkenazi children suffering from TSD in RSA at any one time	0,88 x 4,5 = 4 (approx.)
Maximum estimate of number of Jewish children aged 0 - 4,5 years in RSA	14 000 (approx.)
95% confidence limits of estimated number of TSD sufferers	± 4
∴ there is only a probability of 5% or less that at any one time there are more than 8 Ashkenazi sufferers from TSD in the country	

There are 11 points to consider when discussing a Tay-Sachs screening programme, according to Dr Michael Kaback:

1. Legislation—the programme should be entirely voluntary.
2. Role of the community—the impetus for the programme and the organisation must come from the community, mainly from religious and social groups.
3. Informed consent—individuals requesting investigations must have a clear understanding of what it is all about.
4. Coercion and the right *not* to know—the wishes of certain individuals not to know their carrier status must be respected.
5. Protection of privacy—results of all investigations must be treated as confidential and not be divulged without the subject's consent.
6. Definition of benefits—an educational programme lasting months or even years must precede the screening so that people are made aware of the benefits of such an investigation.
7. Counselling needs—when the results of tests have been communicated to subjects there must be sufficient trained personnel to undertake counselling.
8. Carrier stigmatisation can only be avoided by skilful education before the testing is done and skilful counselling afterwards.
9. Responsibility to other family members—it is hoped that when a carrier has been detected he will feel a sense of responsibility for other family members and encourage them to be tested.
10. Need for psychosocial evaluation and follow-up—with any new venture careful evaluation and follow-up are essential. No individual likes to be told he is 'different' and screening programmes must be modified in the light of the findings.
11. Medical and biological significance of heterozygosity—arguments still rage over the significance of the high Tay-Sachs carrier rate in the Ashkenazi Jews. If it is due to founder effect (one type of random genetic drift) then the gene in the heterozygous state probably has no biological or health significance but if the high rate is due to heterozygote advantage—and there are preliminary data suggesting an advantage conferred against tuberculosis—then attempts must be made to define what this advantage may be.

DOWN'S SYNDROME

It is unnecessary to describe the clinical features of this condition, commonly called mongolism, and now known to be due to a complement of three No. 21 chromosomes instead of the usual two. Approximately 98% of cases are due to a non-disjunction while the remaining 2% are due to an unbalanced translocation state. The former are sporadic, with a marked maternal age effect being apparent, and about half the latter are sporadic, too. About half of the translocation type are familial, with one parent a balanced translocation carrier. It is mandatory to detect these carriers if sound counselling is to be offered and the prevention of the birth to these parents

TABLE V. RISK OF DOWN'S SYNDROME ACCORDING TO MATERNAL AGE*

Maternal age (years)	Risk per 1 000 births
15 - 19	0,43
20 - 24	0,62
25 - 29	0,83
30 - 34	1,15
35 - 39	3,50
40 - 44	9,93
45 - 49	22,00
Total	1,05

* After Collmann and Stoller.[3]

of future children with Down's syndrome achieved.

Table V shows the strong maternal age effect in the production of non-disjunction cases, and it is apparent that certain age groups constitute 'high-risk' populations. Dr Sylvia Johnson of Johannesburg very kindly compiled data on the number of White, Asiatic and Coloured women in South Africa of the various age groups who had babies during 1970 (Table VI). It can be seen that whereas only 2,22% of White women have babies when they are 40 years or older, the corresponding proportions for Asians and Coloureds are 3,8% and 5%, respectively. Presumably the proportion is even higher among our negroid population.

Down's syndrome can be diagnosed with certainty in a 14 - 16-week fetus by karyotyping of cells obtained by amniocentesis. It is, therefore, theoretically possible to diagnose all such cases, and selective abortion of such fetuses could eliminate the condition. At the present stage of technology such a programme is out of the question, but in many centres it may already be feasible to offer such a service to older mothers.

We have made a few calculations based on the number of births for 1970 to Whites, Asiatics and Coloureds in South Africa and the results are presented in Table VII. (If the remainder of the population were to be included the figures would have to be multiplied by 3 to give approximate estimates.) If phase I were directed at a target population of women aged 45 years or older, and if there were a 90% acceptance, then 921 amniocenteses will have to be carried out to diagnose the 22 expected cases of Down's syndrome. If these fetuses were aborted then 8% of the cases of Down's syndrome will have been prevented. A 50% acceptance of the service would result in 12 cases being diagnosed and a 4% prevention rate.

If facilities were available and phase II of the preventive programme could be introduced—with a 90% acceptance—21% of cases of Down's syndrome would be prevented (Table VII). When extended to 35-year-olds and over, 36% of cases could be prevented, but this would require nearly 20 000 amniocenteses per year—an impossibly huge task with our limited resources.

SPINA BIFIDA AND ANENCEPHALY

Multifactorialiy inherited disorders are more common than Mendelian or chromosomal disorders and, among the former, abnormalities of the neural tube are probably the commonest: 7 - 8/1 000 total births in Ulster and Wales, 4/1 000 in South-East England, 2 - 3/1 000 over most of Europe, and less than 2/1 000 in West African and eastern Asian populations.

TABLE VI. BIRTHS TO 'OLDER' MOTHERS IN SOUTH AFRICA, 1970

		Mothers' age			
	Total births	35 - 39 yrs	40 - 44 yrs	45 - 49 yrs	>49 yrs
Whites	**88 886**	**5 479** (6%)	**1 518** (2%)	**161** (0,2%)	**22** (0,02%)
Asiatics	**21 082**	**1 809** (8,6%)	**676** (3%)	**136** (0,6%)	**38** (0,2%)
Coloureds	**74 429**	**7 451** (10%)	**2 986** (4%)	**596** (0,8%)	**140** (0,2%)

TABLE VII. PREVENTIVE PROGRAMME FOR DOWN'S SYNDROME IN SOUTH AFRICA (CALCULATIONS BASED ON BIRTHS FOR 1970)

Phase	Target population (age of pregnant woman)	Number of births*	Number of amniocenteses	Number aborted	% Down's syndrome prevented
I	⩾45	1 093	921 90% accept	22	8
			562 50% accept	12	4
II	⩾40	6 273	5 646 90% accept	60	21
			3 137 50% accept	33	11
III	⩾35	21 012	18 911 90% accept	106	36
			10 506 50% accept	59	20
IV	All ages	184 397	165 957 90% accept	261	90
			92 199 50% accept	145	50

* Whites, Asiatics and Coloureds only.

Empiric risk figures for recurrence after the birth of 1 or 2 children with spina bifida/anencephaly are not available for our population, so we have to counsel patients using figures obtained in other countries. After 1 affected child the recurrence risk is 1 in 20, after 2 affected children, 1 in 10.

A workshop at Vienna was devoted to the management of spina bifida/anencephaly, and a number of clinicians dealt with the subject of contra-indications to active therapy. In Table VIII are summarised Lorber's contra-indications, which include gross paralysis of the legs, extending up into the thoracic region and the presence of hydrocephalus or other gross congenital defects, if present at birth. Even if closure of the defect has been achieved, the subsequent development in the newborn period of meningitis or ventriculitis, in the presence of serious neurological handicap and hydrocephalus, would constitute contra-indications to active therapy. Some workers referred to this approach as the 'judicious management' of the patient.

TABLE VIII. CONTRA-INDICATIONS TO ACTIVE THERAPY OF MYELOMENINGOCELE

At birth
- **Gross paralysis of the legs**
- **Thoracolumbar or thoracolumbosacral lesions**
- **Kyphosis or scoliosis**
- **Grossly enlarged head (2 cm or more > 90th percentile)**
- **Intracerebral birth injury**
- **Other gross congenital defects (e.g. cyanotic heart disease, ectopia of bladder)**

After closure, in newborn period
- **Meningitis or ventriculitis when there is serious neurological handicap and hydrocephalus**

Later
- **In any life-threatening episode in a child who is severely handicapped by gross mental and neurological defects**

Lorber, Sheffield

Renwick's 'blighted potato' hypothesis as a factor in the causation of spina bifida/anencephaly did not receive any attention. Methods for detecting neural tube malformations *in utero*, thereby enabling selective abortions to be carried out, include:

Fetoscopy. The technique was reviewed and although spectacular successes were not reported, it would seem as though within the next few years, instrumentation may improve to a sufficient extent to permit its use for detecting abnormalities before 20 weeks' gestation.

Ultrasound detection of anencephaly at 17 weeks' gestation has been made, and Campbell of Queen Charlotte's Hospital, London, reported some conspicuous successes obtained with this technique. He said that 50% of women attending their antenatal clinic were now subjected to the examination.

Alpha-fetoprotein. A significant advance in the diagnosis of neural tube abnormalities was reported about a year ago when David Brock, working in Edinburgh, observed a raised level of α-fetoprotein in the amniotic fluid of fetuses subsequently born with spina bifida. Dr Ferguson Smith reported the first two successful prospective diagnoses.

Brock *et al.*[1] reported an anencephalic pregnancy first diagnosed by measurement of α-fetoprotein in maternal serum at 16 weeks' gestation. There are obvious difficulties in introducing this sort of screening test (levels are raised in many conditions unrelated to pregnancy, and in threatened abortion, non-specific cases of fetal distress and intra-uterine death) but if a raised maternal serum level of α-fetoprotein were simply employed to detect these patients needing amniocentesis and the measurement of α-fetoprotein levels in amniotic fluid, then a great advance in the detection of this tragic disease will have been made.

CONCLUSION

It is impossible in the space available to give a comprehensive account of the Fourth International Conference on Birth Defects and I have instead concentrated on one theme—the prevention of hereditary diseases.

The questions considered affect each one of us, if we take our responsibilities to society at all seriously. Moral and ethical issues are raised by almost every 'preventive' measure discussed. The 'judicious management' of children with meningomyelocele is a euphemism for killing the child with a bad prognosis; amniocentesis and selective abortion a euphemism for killing the fetus with a genetic disease. Concerned people—geneticists, paediatricians, and obstetricians, as well as theologians, philosophers and lawyers, need to be convened in South Africa to discuss these problems, if we are not to be left behind.

A few months ago the Southern African Inherited Disorders Association was formed. This is a lay/medical organisation, one of whose aims is the education of the public in the field of inherited diseases and it is suggested that a discussion of the moral issues in medical genetics should be one matter to which it might draw public attention.

Medical genetics has come a long way in a relatively short time. Even though there are many problems still awaiting solution it can be claimed that during the past 3 years or so some 'giant steps' have been taken and the way is now clear to deal effectively with a significant number of hereditary diseases.

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REFERENCES

1. Brock, D. J. H., Bolton, A. E. and Monaghan, J. M. (1973): Lancet, **2**, 923.
2. Scriver, C.R. (1969): Brit. Med. Bull., **25**, 35.
3. *Idem* (1971): In *Proceedings of the XIII International Congress of Pediatrics, Vienna*, vol. V, pp. 191 - 195. Amsterdam: Excerpta Medica.
4. O'Brien, D. and Goodman, S.I. (1970): Pediatrics, **46**, 620.
5. Jenkins, T., Lehmann, H. and Nurse, G. T. (1974): Brit. Med. J., **2**, 23.
6. Clow C. L., Fraser, F. C., Laberge, C. and Scriver, C. R. *in* Steinberg, A. G. and Bearn, A. G., eds (1973): *Progress in Medical Genetics*, vol. ix, pp. 159 - 213. New York: Grune & Stratton.
7. Motulsky, A. G., Fraser, G. R. and Felsenstein, J. (1971): *Birth Defects* (Original Article Series VII) No. 5, pp. 22 - 32. New York: March of Dimes.
8. Collmann, R. D. and Stoller, A. (1962): Amer. J. Publ. Hlth, **52**, 813.