Genetic counselling and family practice

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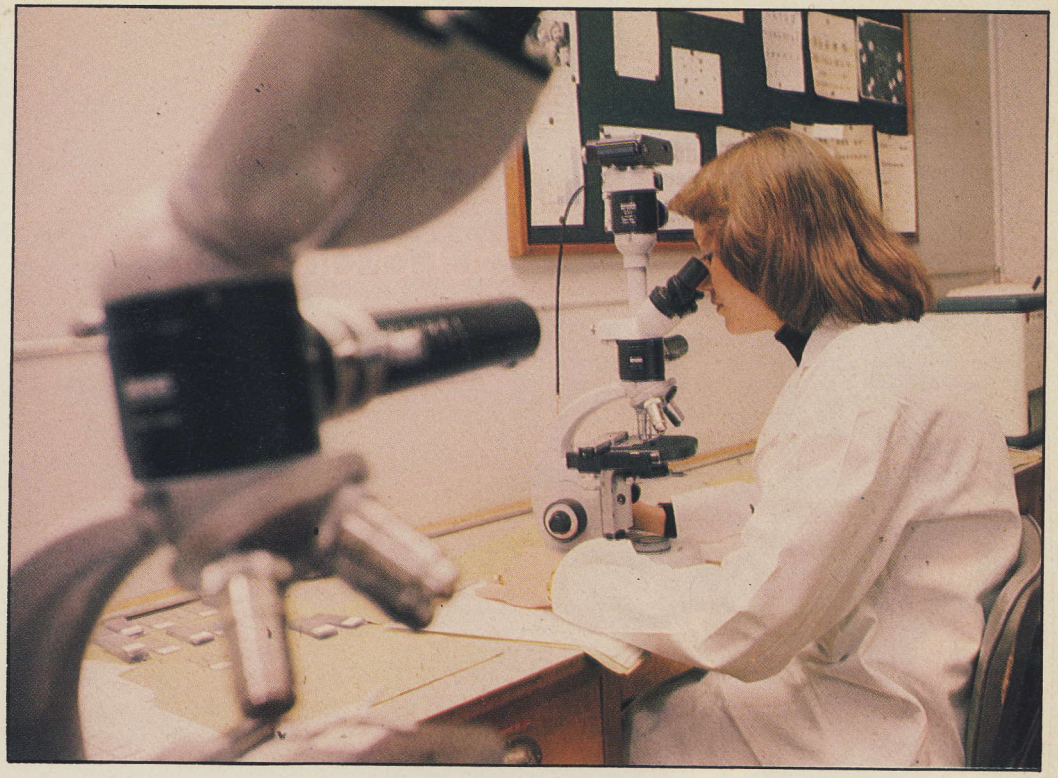

Examples of the more common chromosomal defects according to numerical, structural and mosaic anomalies are listed in table 6.

For many years cytogeneticists had to rely on the gross morphology such as size, position of centromere and secondary constrictions to detect specific chromosomal anomalies.

Modern banding techniques have recently (1968) been developed by which a much greater differentiation between chromosomes can be attained and previously undetected defects are now identifiable. Examples of specific banding patterns are depicted in Fig. 1.

Table 6 RECOGNISABLE CHROMOSOMAL ANOMALIES

Chromosomal anomally	Common name	Overall frequency in live births
Numerical		
47, XX or XY, +21	Down syndrome	1:660
47, XX or XY, +18	Edward syndrome	0.3:1,000
47, XX or XY, +13	Patau syndrome	1:5,000
74, XXY	Klinefelter syndrome	1:500 males
45, X	Turner syndrome	0.4:1,000 females
Structural		
46, XX or XY, 5p	Cri du chat syndrome	Rare
46, XX or XY, 4p	Wolf-Hirschhorn syndrome	Rare
46, XX or XY, 3q+	3q+syndrome	Rare
46, XX or XY, t(DqGq)	Down syndrome	3.5 % of all Down syndromes
46, XX or XY, 18p-	18p- syndrome	Rare
46, XX or XY, 18q-	18q- syndrome	Rare
Mosaicism		
46, XX or XY/47, XX or XY, +21	Down syndrome	1 to 2 % of all Downs
46, XX/45, X	Turner syndrome	7 to 10 % of all Turner syndrome cases
45, X/46, XX/47, XX, +21	Turner/Down mosaic syndrome	Very rare
45, X/46, X, +21	Turner/Down mosaic syndrome	Very rare
47. XXY/46, XY	Klinefelter syndrome	15 % of all Klinefelter syndrome cases

Fig. 1
C-Banding Q " — G
N-Banding R - " T "

Recent advances have revealed that Down syndrome which is associated with mental retardation and which is by far the most common chromosomal defect has three or more different chromosomal causes:

1 Primary trisomy 21 (95 per cent of cases)
2 Translocation of chromosome 21 onto another chromosome, often chromosome 14 (3 - 4 per cent of cases)
3 Mosaicism, which is the result of mitotic nondisjunction. Such an individual has both normal and trisomy 21 cells (1 - 2 per cent of cases).

Various theories underly the cause of the different chromosomal aberrations. Most significant is that of maternal age which is associated with the primary trisomies especially Trisomy 21 (figure 2).

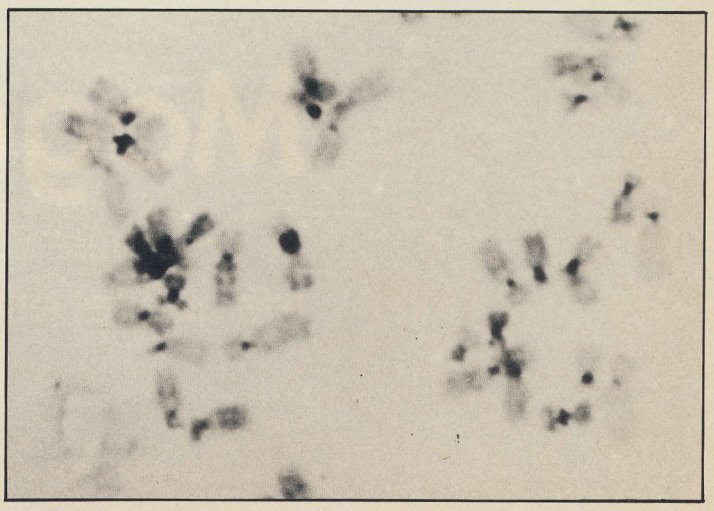

Figure 2

Incidence of down syndrome at birth and of fetal chromosomal abnormalities at amniotocentesis, by maternal age

Maternal Age	Down Syndrome At Birth	Maternal Age	Down Syndrome At Second Trimester		Total Aneuploidies At Second Trimester	
15-19	1/682[a]					
20-24	1/1352					
25-29	1/1133					
30	1/885					
31	1/826					
32	1/725					
33	1/592					
34	1/465					
35	1/365					
36	1/287	35-36	0[b]		1/143[c]	
36	1/287	35-36	0[b]	1/143[b]	1/104[b]	1/66[b]
37	1/225					
38	1/176	37-38	1/128	1/100	1/48	1/54
39	1/139					
40	1/109	39-40	1/149	1/45	1/75	1/35
41	1/85					
42	1/67	41/42	1/32	1/41	1/23	1/31
43	1/53					
44	1/41	43/44	1/18	1/18	1/14	1/10
45	1/32					
46	1/25					

a. Hook, E.B., Lindsjo, A.: Down Syndrome In Live Births by Single Year Maternal Age Interval in a Swedish Study: Comparison with Results from a New York Study. Am J Hum Genet 30: 19-27, 1978.

b. Hook, E.B.: Differences between rates trisomy 21 Down syndrome (DS) and other crhomosomal abnormality diagnosis in live births and in cell culture 2nd trimester amniocentesis: Suggested explanations for genetic counselling and program planning. Birth Defects, 14: (6c): 249, 1978.

c. Colbus, M., Laugham, W., et al: Prenatal genetic diagnosis in 3000 amniocentesis. New Engl J Med, 300: 157, 1979.

Chromosomal analysis is essential in all cases of Down syndrome especially to determine which cases are the translocation type since 50 per cent of the translocation types, are familial with an average recurrence risk of 10 - 15 per cent if a parent is a translocation carrier. The remaining 50 per cent of the translocation cases occur de novo.

Translocation and trisomy 21 types of Down syndrome are clinically similar whereas the clinical symptoms in the mosaic type are less severe.

Since chromosome investigations are expensive and time consuming, care should be taken that only those cases are referred where a firm indication for a chromosome analysis exists (Table 7).

Table 7 Indications for chromosomal analyses

1 Confirmation of suspected chromosomal syndromes (e.g. Down's Turner's, etc.)
2 Infants of parents who are translocation carriers.
3 Multiple congenital anomalies of unknown aetiology.
4 Parents of children with mental retardation and multiple congenital anomalies of unknown aetiology.
5 Ambiguous external genitalia.
6 Girls with peripheral lymphaedema.
7 Cryptorchidism.
8 Grils with inguinal mass
9 Poor reproductive fitness — sterility, abortion, prenatal mortality.
10 Sex chromatin count not consistent with the phenotypic sex.
11 Low sex chromatin counts and multiple or abnormal sex chromatin.
12 Maternal age 40 years and older (amniocentesis).

Chromosomal analyses are particularly useful in determining the cause of mental retardation in patients with dysmorphic physical features of unknown morphology.

BIOCHEMICAL GENETICS

As far back as 1908 Garrod introduced the term "inborn errors of metabolism" when describing the four inherited metabolic disorders: albinism, cystinuria, pentosuria and alkaptonuria.

Since then, more than 200 metabolic disorders have been identified. Although the general incidence of metabolic disorders is relatively low (e.g. P.K.U., 1 in ± 10 000 births), the importance of early detection of some e.g. Hyperlipidaemia (1 in 50) or Porphyria variegata (1 in 300 Afrikaners) is self explanatory.

These disorders are mostly inherited as autosomal recessive conditions and are usually due to a defective gene resulting in a defective or deficient gene product in the metabolic pathways of the metabolic or anabolite.

The consequences are:

1 No metabolites are produced beyond the block.
2 Substances proximal to the block accumulate
3 Alternate pathways are implicated

The consequence is a clinical effect which is related to the importance of the relevant compound which occurs either in excess or is deficient. This may be expressed as a functional deficit and even as structural change e.g. mental retardation or gross morphological changes e.g. in the mucopolysaccharidoses.

In most cases the inherited metabolic defect can be identified by measuring the accumulated or deficient metabolite, or directly the defective enzyme such as hexosaminidates — A in Tay-Sachs disease or haemoglobin in sickle cell anaemia.

In other cases the diagnosis is facilitated by measuring a compound or enzyme several steps removed from the basic enzyme defect.

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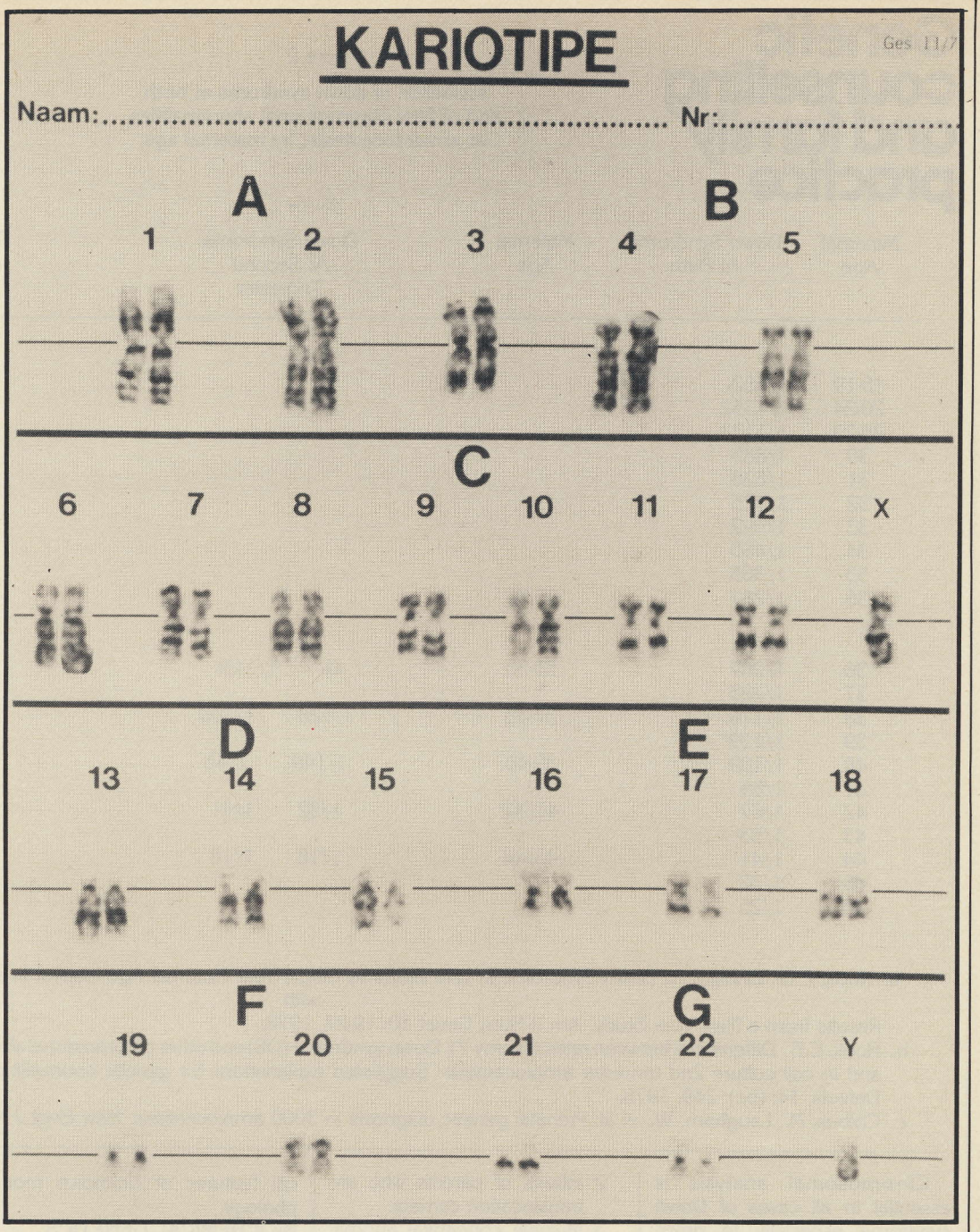

Cystic fibrosis is diagnosed by means of a sweat test. Raised albumin in the meconium provided a method for neonatal screening but the primary biochemical defect is still unknown.

Table 8 INDICATIONS FOR THE DIAGNOSIS OF INHERITED METABOLIC DEFECTS

1 Failure to thrive and/or CNS deterioration.
2 Unexplained metabolic changes — dehydration acidosis
3 Unusual urine odour
4 Skin and hair changes
5 Neurological disorders
6 Unexplained visceromegaly, renal or cardiac failure
7 Organomegaly e.g. macroglossia, coarse facial features, or gingival hyperplasia
8 Abnormal response to drugs
9 Renal Colic or calculus

Understanding the precise biochemical defect in certain metabolic disorders has facilitated methods for corrective treatment (Table 9).

Table 9 TREATMENT OF INBORN ERRORS OF METABOLISM

Exclusion of toxic foods

Galactosaemia; elimination of dietary galactose Type I hyperlipidaemia; exclusion of neutral fats from diet Refsum's disease; elimination of dietary phytanic acid Favism: exclusion of fava beans from diet

Restrictions of toxic foods

Phenylketonuria: controlled phenylalanine intake
Maple syrup urine disease: controlled intake of branched-chain amino acids
Hereditary tyrosinaemia: controlled tyrosine intake

Supplementation of diet for deficiency state

Phenylketonuria: high-tyrosine diet
Isovalericacidaemia: high-glycine diet
Arginiosuccinicaciduria: high-arginine diet

Supplementation of vitamins

Methyltetrahydrofolate reductase deficiency:
folic acid supplementation
Methyltetrahydrofolate transferase deficiency:
folic acid supplementation
B_{12}-responsive methylmalonicacidaemia: vitamin B_{12} supplementation
B_{12}-responsive homocystinuria with methylmalonicaciduria:
vitamin B_{12} supplementation
B_6-responsive cystathionine synthase deficiency:
vitamin B_6 supplementation

Adapted from Hsia, Y.E., Treatment in Genetic Diseases, in Milunsky, A. (ed), The Prevention of genetic Disease and Mental Retardation, Philadelphia: W.B. Saunders, 1975, pp. 227-305.

PRENATAL DIAGNOSIS OF GENETIC DEFECTS

Until recently genetic counselling was based on numerical risk calculations.

With the development of amniocentesis and other prenatal diagnostic procedures (Table 10) which have become possible with the advances in biochemical genetics and obstetric procedures, a near 100 per cent certainty in a prenatal diagnosis can be reached.

Table 10 METHODS OF PRENATAL DIAGNOSIS TECHNIQUES

Direct (Getal)

1 Radiography
1.1 Skeletal
1.2 Soft tissues (amniography, feotography)
2 Sonography
3 Electrocardiography
4 Foetoscopy
5 Biopsy
5.1 Membranes
5.2 Placenta
5.3 Foetus
6 Amniocentesis

Indirect (Maternal)

1 Blood e.g. foetal lymphocytes
2 Urine e.g. oestriol excretion

The implication of prenatal diagnosis is that termination of pregnancy is indicated in the case of a positive diagnosis.

Since prenatal diagnosis is not the cheapest and the fact that a risk is involved in the mere physical procedure (1 %) necessitates that certain criteria are met before a woman becomes eligible for prenatal diagnosis.

Criteria for prenatal diagnosis

— A diagnostic test in the prenatal period must be available for the disorder concerned
— the disorder must be sufficiently serious to justify termination of pregnancy
— Treatment must be inadequate or absent
— Risk to a particular pregnancy must considerable
— Termination of pregnancy must be acceptable to couple concerned

Anniocentesis has become the most widely used method in prenatal diagnosis and involves the following:

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1 Pre-amniocentesis counselling
2 Sonography to determine gestational age and the localization of the foetus and placenta
3 Local anaesthesia, if necessary
4 Introduction of amniocentesis needle to withdraw + 10 ml of clear amniotic fluid

The procedure is painless and local anaesthesia is seldom necessary. A counselling session prior to amniocentesis is advisable where the implications, and possible complications as well as the benefits can be explained to the couple. Amniocentesis for genetic diagnosis is usually performed at 14-16 weeks of gestation.

Tests may either be performed directly on amniotic fluid or from cultured cells obtained from the fluid.

Due to limited facilities, costs and risks, only selected cases can be considered for amniocentesis. There are specific indications for when an amniocentesis should be done (Table 11)

Table 11: INDICATIONS FOR AMNIOCENTESIS

1 Previous child with a chromosomal abnormality
2 Parent a carrier of a chromosomal aberration
3 A child or parent (first degree relative) with a neural tube defect
4 Both parents carriers of a diagnosable autosomal recessive disorder diagnosable prenatally
5 Advanced maternal age — 40 and older
6 Mother an obligate carrier of a serious X-linked recessive disorder

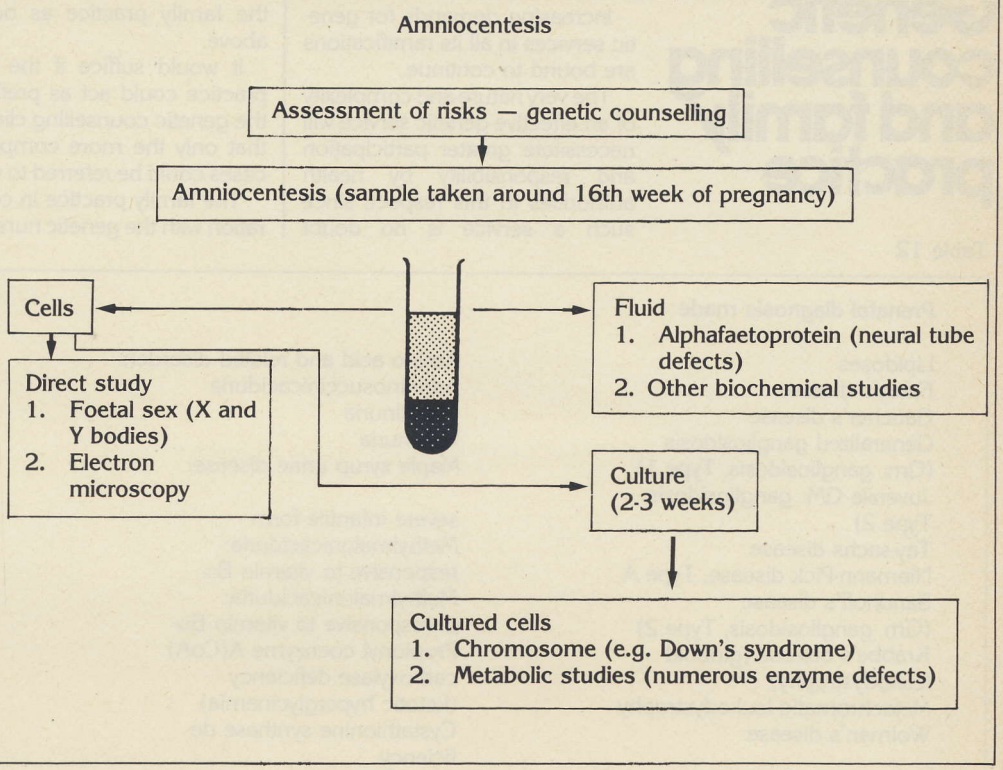
The following disorders can be diagnosed by amniocentesis

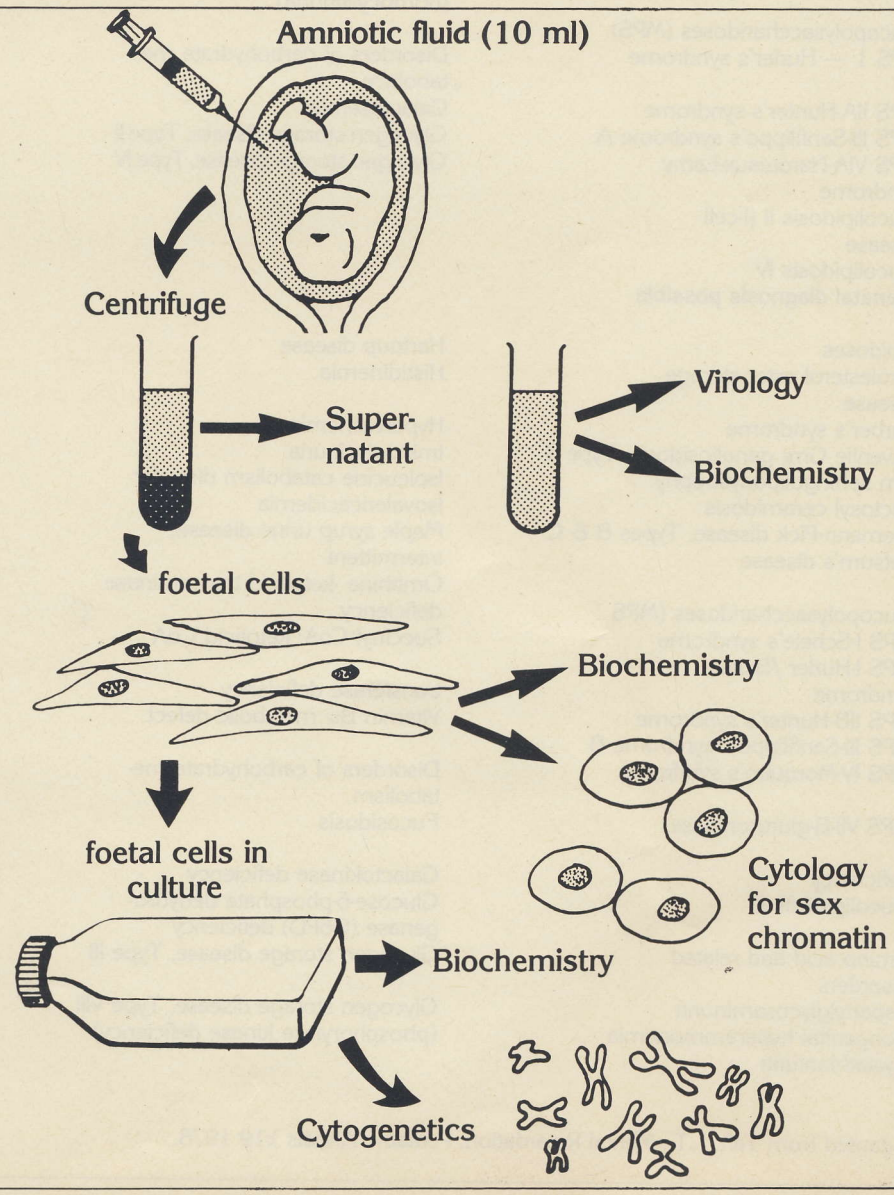
Defect diagnosable by amniocentesis

— All chromosomal defects
— About 100 metabolic disorders
— 90 % of neutral tube defects (open types)

Metabolic disorders diagnosable by amniocentesis or other prenatal diagnostic method include the following (Table 12).

Fig. 3 Scheme of diagnostic procedure in amniocentesis





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FINAL COMMENT

Increasing demands for genetic services in all its ramifications are bound to continue.

The very nature and complexity of an effective genetic service will necessitate greater participation and responsibility by health authorities in this respect, since such a service is no doubt community orientated.

An effective service cannot function without the assistance of the family practice as outlined above.

It would suffice if the family practice could act as prefilter to the genetic counselling clinics so that only the more complicated cases could be referred to clinics.

The family practice in collaboration with the genetic nurses can provide a facility through which the family concerned can obtain a comprehensive service.

The demands for genetic counselling increase and more agencies and facilities are becoming involved. In the light of this and the greater awareness of the responsibility towards the implications of genetic counselling, it is essential that attention be paid to the ethical issues.

Table 12

Prenatal diagnosis made

Lipidoses
Fabry's disease
Gaucher's disease
Generalized gangliosidosis
(Gm1 gangliosidosis, Type 1)
Juvenile GM1 gangliosidosis,
Type 2)
Tay-sachs disease
Niemann-Pick disease, Type A
Sandhoff's disease
(Gm gangliosidosis, Type 2)
Krabbe's disease (globoid
leukodystrophy)
Metachromatic leukodystrophy
Wolman's disease

Mucopolysaccharidoses (MPS)
MPS 1 — Hurler's syndrome

MPS IIA-Hunter's syndrome
MPS III-Sanfilippo's syndrome A
MPS VIA-Naroteaux-Lamy
syndrome
Mucolipidosis II (I-cell
disease
Mucolipidosis IV

Amino acid and related disorders
Agrininosuccinicaciduria
Citrullinuria
Cystinuria
Maple syrup urine disease:

severe infantile form
Methylmalonicaciduria:
responsive to vitamin B12
Methylmalonicaciduria:
unresponsive to vitamin B12
Propionyl coenzyme A(CoA)
carboxylase deficiency
(ketotic hyperglycinemia)
Cystathionine synthase de-
ficiency
(homocystinuria)

Disorders of carbohydrate me-
tabolism
Galactosemia
Glycogen storage disease, Type II
Glycogen storage disease, Type IV

Miscellaneous hereditary disorders
Adenosine deaminase (ADA)
deficiency
Congenital nephrosis
Cystinosis (Fanconi's syndrome)

Hypophosphatasia
Lesch-Nyhan syndrome
Lysosomal acid phosphatase
deficiency
Thalassemia (a and b)
Xeroderma pigmentosum
Duchenne muscular dystrophy
Adrenogenital syndrome
(21-hydroxylase deficiency)
Sickle cell anemia

Hemophilia A
Acute intermittent porphyria

Menkes' disease

Prenatal diagnosis possible

Lipidoses
Cholesterol ester storage
disease
Farber's syndrome
Juvenile Gm2 gangliosidosis, Type 3
Gm sphingolipodystrophy
Lactosyl ceramidosis
Niemann-Pick disease, Types B & C
Refsum's disease

Mucopolysaccharidoses (MPS
MPS I-Scheie's syndrome
MPS I-Hurler /Scheie
syndrome
MPS IIB-Hunter's syndrome
MPS III-Sanfilippo's syndrome B
MPS IV-Morquiro's syndrome

MPS VII-B-glururonidase

deficiency
Mucolipidosis III

Amino acid and related
disorders
Aspartylglycosaminuria
Congenital hyperammonemia
Cystathioniuria

Hartnup disease
Histidinemia

Hypervalinemia
Iminoglycinuria
Isoleucine catabolism disorder
Isovalericacidemia
Maple syrup urine disease:
intermittent
Ornithine -ketoacid transaminase
deficiency
Succinyl CoA: ketoacid CoA

transferase deficiency
Vitamin B12 metabolic defect

Disorders of carbohydrate me-
tabolism
Fucosidosis

Galactokinase deficiency
Glucose-6-phosphate dehydro-
genase (G6PD) deficiency
Glycogen storage disease, Type III

Glycogen storage disease, Type VIII
(phosphorylase kinase deficiency)

Mannosidosis
Glucose phosphate isomerase

deficiency
Pyruvate decarboxylase deficiency
Pyruvate dehydrogenase deficiency
Miscellaneous hereditary disorders
Acatalasia
Chediak-Higashi syndrome

Congenital erythropoietic
porphyria

familial hypercholesterolemia
Glutathionuria
Leigh's encephalopathy
Lysyl-protocollagen hydroxylase

deficiency

Nail-patella syndrome
Protoporphyria

Saccharopinuria

Testicular feminization
Myotonic dystrophy

Adapted from Taft, L.T.: Mental Retardation, Pediatric Annals);19 1978.

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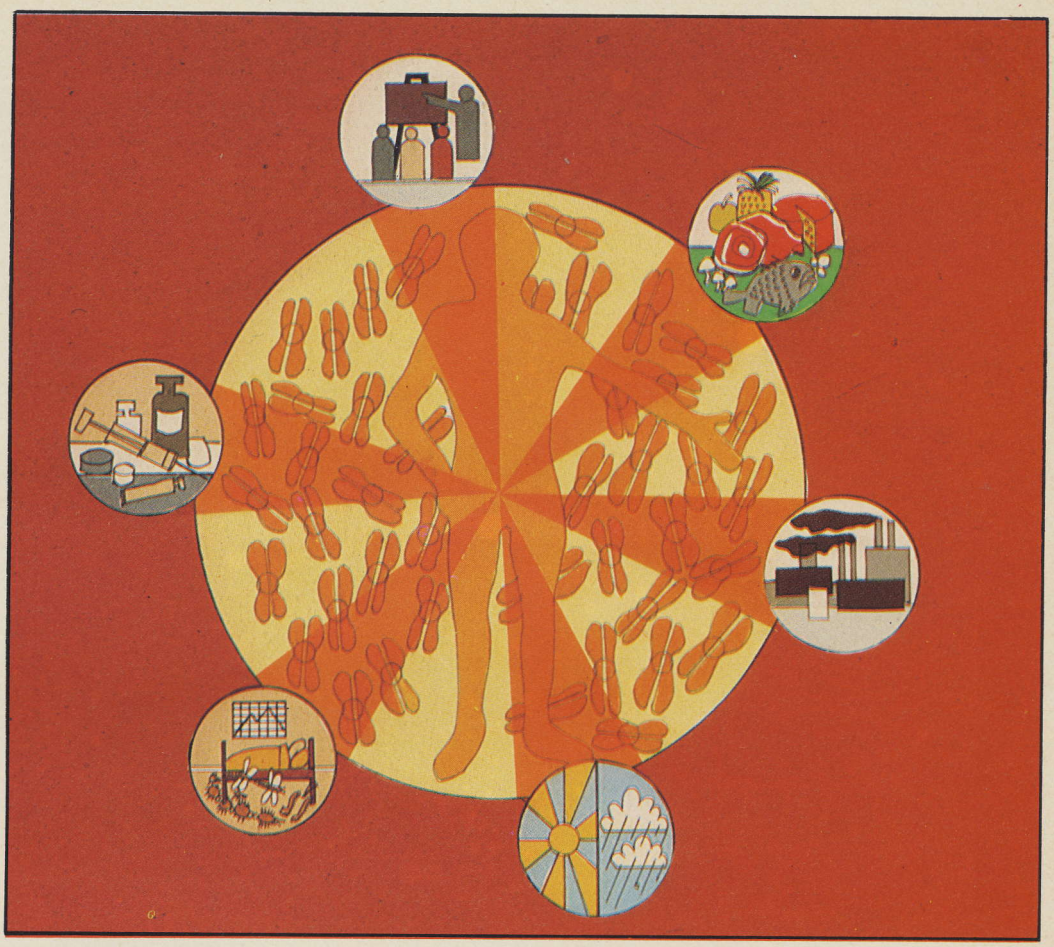
ABOUT THE AUTHOR

Johan Op't Hof completed a B.Sc. in genetics at Stellenbosch in 1962 before joining the Human Sciences Research Council where he undertook research on Hereditary Blindness.

In 1968 he completed his M.Sc. before continuing with human genetics at the Medical School of the University of Feibung in Germany.

On completing a D.Sc. degree in 1970 he acknowleged a request from the Dept of Health to start a genetic service in the Department of Health.



Health.

The service only got off the ground in 1975 and was formally instituted in 1977. In the meantime most of us have had some contact with Genetic Services and hopefully shared in the benefits involved.

Johan has been to the USA, Canada, Edinburgh, Germany, Belgium and Holland to study Genetic Services.