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

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

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).
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 1.0–1.5 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

<table>
<thead>
<tr>
<th>Maternal Age</th>
<th>Down Syndrome At Birth</th>
<th>Maternal Age</th>
<th>Down Syndrome At Second Trimester</th>
<th>Total Aneuploidies At Second Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-19</td>
<td>1/672</td>
<td>35-36</td>
<td>0b</td>
<td>1/143:</td>
</tr>
<tr>
<td>20-24</td>
<td>1/1352</td>
<td>35-36</td>
<td>1/104:</td>
<td>1/66:</td>
</tr>
<tr>
<td>25-29</td>
<td>1/1133</td>
<td>37-38</td>
<td>1/128</td>
<td>1/100:</td>
</tr>
<tr>
<td>30</td>
<td>1/885</td>
<td>39-40</td>
<td>1/149</td>
<td>1/45:</td>
</tr>
<tr>
<td>31-32</td>
<td>1/725</td>
<td>41-42</td>
<td>1/32</td>
<td>1/41:</td>
</tr>
<tr>
<td>33</td>
<td>1/592</td>
<td>43-44</td>
<td>1/18</td>
<td>1/18:</td>
</tr>
<tr>
<td>34</td>
<td>1/465</td>
<td>45-46</td>
<td>1/14</td>
<td>1/10:</td>
</tr>
<tr>
<td>35</td>
<td>1/365</td>
<td>36-37</td>
<td>1/287</td>
<td>1/225:</td>
</tr>
<tr>
<td>36</td>
<td>1/287</td>
<td>38-39</td>
<td>1/176</td>
<td>1/139:</td>
</tr>
<tr>
<td>37</td>
<td>1/225</td>
<td>40-41</td>
<td>1/109</td>
<td>1/45:</td>
</tr>
<tr>
<td>38</td>
<td>1/176</td>
<td>42-43</td>
<td>1/85</td>
<td>1/32:</td>
</tr>
<tr>
<td>39</td>
<td>1/139</td>
<td>44-45</td>
<td>1/67</td>
<td>1/41:</td>
</tr>
<tr>
<td>40</td>
<td>1/109</td>
<td>46-47</td>
<td>1/53</td>
<td>1/41:</td>
</tr>
<tr>
<td>41</td>
<td>1/85</td>
<td>48-49</td>
<td>43-44</td>
<td>1/18:</td>
</tr>
<tr>
<td>42</td>
<td>1/67</td>
<td>50-51</td>
<td>45-46</td>
<td>1/14:</td>
</tr>
<tr>
<td>43</td>
<td>1/53</td>
<td>52-53</td>
<td>36-37</td>
<td>1/287:</td>
</tr>
<tr>
<td>44</td>
<td>1/41</td>
<td>54-55</td>
<td>38-39</td>
<td>1/176:</td>
</tr>
<tr>
<td>45</td>
<td>1/32</td>
<td>56-57</td>
<td>40-41</td>
<td>1/109:</td>
</tr>
<tr>
<td>46</td>
<td>1/25</td>
<td>58-59</td>
<td>42-43</td>
<td>1/85:</td>
</tr>
</tbody>
</table>


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.
5. Ambiguous external genitalia.
6. Girls with peripheral lymphoedema.
7. Cryptorchidism.
8. Girls 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 inherent 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. Hypothyroidism (1 in 2000) or Phenylketonuria (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 anabolic.

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 hexosaminidases - 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.
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. 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
  - 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
  - Isovalericacidemia: high-glycine diet
  - Argininosuccinic aciduria: high-arginine diet

- Supplementation of vitamins
  - Methyltetrahydrofolate reductase deficiency: folic acid supplementation
  - Methyltetrahydrofolate transmethylation: folic acid supplementation
  - B12-responsive homocystinuria with methylmalonicaciduria: vitamin B12 supplementation
  - B12-responsive cystathionine synthase deficiency: vitamin B12 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.

**Table 10** METHODS OF PREGNATAL DIAGNOSIS TECHNIQUES

**Direct (Getical)**
1. Radiography
2. Skeletal
3. Soft tissues (amniography, fetography)
4. Sonography
5. Biopsy
6. Foetoscopy
7. Membranes
8. Placenta
9. Foetus
10. 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 be considered
- Termination of pregnancy must be acceptable to couple concerned

Amniocentesis has become the most widely used method in prenatal diagnosis and involves the following:
Genetic counselling and family practice

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

- All chromosomal defects
- About 100 metabolic disorders
- 90% of neural tube defects (open types)

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

<table>
<thead>
<tr>
<th>Prenatal diagnosis possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipidoses</td>
</tr>
<tr>
<td>Fabry’s disease</td>
</tr>
<tr>
<td>Gaucher’s disease</td>
</tr>
<tr>
<td>Generalized gangliosidosis</td>
</tr>
<tr>
<td>(Gm gangliosidosis, Type 1)</td>
</tr>
<tr>
<td>Juvenile Gm gangliosidosis, Type 2)</td>
</tr>
<tr>
<td>Tay-Sachs disease</td>
</tr>
<tr>
<td>Niemann-Pick disease, Type A</td>
</tr>
<tr>
<td>Sandhoff’s disease</td>
</tr>
<tr>
<td>(Gm gangliosidosis, Type 2)</td>
</tr>
<tr>
<td>Krabbe’s disease (globoid leukaodystrophy)</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
</tr>
<tr>
<td>Wolman’s disease</td>
</tr>
<tr>
<td>Mucopolysaccharidoses (MPS)</td>
</tr>
<tr>
<td>MPS I – Hurler’s syndrome</td>
</tr>
<tr>
<td>MPS II-Hunter’s syndrome</td>
</tr>
<tr>
<td>MPS III-Sanfilippo’s syndrome A</td>
</tr>
<tr>
<td>MPS VIA-Naroteau-Lamy syndrome</td>
</tr>
<tr>
<td>Mucolipidosis II (I-cell disease)</td>
</tr>
<tr>
<td>Mucolipidosis IV</td>
</tr>
</tbody>
</table>

Amino acid and related disorders
- Agrininosuccinicaiduria
- Citrullinuria
- Cystinuria
- Maple syrup urine disease:
  - severe infantile form
  - Methylmalonicaciduria: responsive to vitamin B12
  - Methylmalonicaciduria: unresponsive to vitamin B12
  - Propionyl coenzyne A(CoA) carboxylase deficiency
  - (ketotic hyperglycemia
  - Cystathionine synthase deficiency
    - (homocystinuria)
- Disorders of carbohydrate metabolism
  - 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
- Leish-Pyhan syndrome
- Lysosomal acid phosphatase deficiency
- Thalassemia (a and b)
- Xeroderma pigmentosum
- Duchenne muscular dystrophy
- Adrenogonadal syndrome
  - (21 hydroxylase deficiency)
- Sickle cell anemia
- Hemophilia A
- Acute intermittent porphyria
- Menkes’ disease
- 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-protoecollagen hydroxylase deficiency
- Nail-patella syndrome
- Protoporphyria
- Saccharopinuria
- Testicular feminization
- Myotonic dystrophy

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

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