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A Short Textbook of Paediatrics

Pincus Catzel

A SHORT TEXTBOOK OF
PAEDIATRICS

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A SHORT TEXTBOOK OF PAEDIATRICS

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EDITOR'S FOREWORD

Recent years have seen the word paediatrics shunned by most doctors and the term child health used in its stead, but I doubt if there has really been such a decisive swing from the treatment of established disease to its prevention.

By far the greatest number of babies and children in the world today are only taken to the doctor or nurse when ill health has already appeared. Therefore a really first class simple guide to diagnosis and treatment is in great demand and this is precisely what Doctor Catzel offers us here.

The author who has worked in Pretoria and latterly Johannesburg has also spent many years in Great Britain. He is responsible for that popular and very practical little book, *The Paediatric Prescriber*. His simple, direct style of writing and skilful compression of the material will commend him to the student who is already overloaded by the present day medical syllabus.

This book is written primarily for the men and women who want to know how to examine, diagnose and treat sick children. It succeeds admirably and I believe it will not be long before a new edition is demanded.

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Pincus Catzel

AUTHOR'S PREFACE

When Oribasius (AD 325–403) physician to Emperor Julius the Apostate attempted to summarize the works of Galen he reduced the work to 70 volumes. By further omission of all anatomical and surgical references and reducing the work from a summary to an abstract, he was left with 9 volumes. Even this was considered by the physicians of the time to be too long.

In preparing this short textbook one is acutely aware of Oribasius's dilemma. Anatomical and surgical references have been made only in passing, while the other two rocks on which paediatrics is based, physiology and pathology have received scant attention. The vast field of antenatal paediatrics has been mentioned—but only just—and the field of neonatology which deserves 9 volumes on its own has been compressed into a chapter or two. Scant attention has been paid to the normal child and reference must therefore be made to the works of Gesell, Illingworth and many others. Today if the student wishes to study the *Biological Basis of Pediatric Practice*, Cooke's book of this title will serve as an introduction but it is 1739 pages long and has a 76 page index. Standard textbooks of paediatrics such as those of Nelson or of Barnett run to 1500 and 2000 pages respectively, not to mention the innumerable volumes on tropical paediatrics, paediatric diagnosis, paediatric pathology, allergy, endocrine and genetic diseases of childhood and paediatric surgery. Paediatric cardiology alone can boast at least 70 volumes, while paediatric therapy is served by at least two large volumes, that of Shirkey and of Gellis and Kagan, in addition to the smaller *Paediatric Prescriber*. Indeed any respectable paediatrician can probably count 70 volumes related exclusively to paediatrics, in addition to those marvellous Year Books, the Pediatric Clinics of North America and heavens knows how many dozens of journals in his own personal library. Medical school libraries must have at least ten times that number.

It is thus with humble acknowledgment of this vast, almost overwhelming field that I offer this small work for students and practitioners who require a brief review of clinical paediatrics. I have tried to emphasize common conditions which I think it is important to know well, but have also mentioned rare conditions which I believe have something important to teach.

Pincus Catzel

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1

HUMAN GENETICS

The child is the end-product of the clash between his genetic constitution and his environment. If his genetic constitution is weak, e.g. in Down's syndrome or cystic fibrosis, he may not be able to survive unless he is specially protected. On the other hand, no matter how brilliant his inheritance, it cannot reach fruition unless it is tenderly nurtured and cared for.

It is necessary therefore that the practitioner learn the language of human genetics so that he can advise parents who are afflicted with an abnormal child. Genetic counselling demands a great deal of knowledge, patience and human understanding. It should only be undertaken by practitioners with a special interest in the subject.

Congenital abnormalities are abnormalities that can be detected at birth, e.g. hare-lip; or shortly thereafter, e.g. congenital deafness, cataracts, congenital hypertrophic pyloric stenosis or renal tract anomalies. Many congenital anomalies are transmitted according to the laws of Mendelian inheritance. In some of these a definite chromosomal abnormality can be detected, but in others it can not. Other congenital anomalies are not inherited but are caused by damage to the embryo in the first trimester of pregnancy by a virus such as *rubella* or *cytomegalovirus*, a parasite such as *Toxoplasma gondii* or drugs such as thalidomide or cytotoxic agents. None of these conditions can be reversed by treatment, though some can be prevented, e.g. rubella can be prevented by vaccination of all fertile females who have never previously contracted the disease. Greater care in the use of drugs in early pregnancy may prevent other abnormalities.

Chromosomes are the bearers of the hereditary material known as genes. The genes are linearly arranged along the chromosome, each occupying a specific locus. Each gene is made up of deoxyribonucleic acid (DNA) whose nucleotide bases guanine, cystosine, adenine and thymine are arranged in sequences known as the 'triplet code'. This sequence forms the template for RNA, which transfers the 'message' from the chromosome in the nucleus, to the ribosome in the cell's protoplasm, and interprets it in the form of an amino-acid sequence. The amino acids are built up to form enzymes and other proteins.

The Watson-Crick model pictures the DNA in the form of a double helix. When the cell divides, the helix unwinds and reduplicates itself (mitosis)

so that two complete cells with two complete sets of paired chromosomes are formed. During *sexual* division (meiosis) reduplication does not occur and each sex cell then holds only one half of the chromosome material. An *autosome* is any chromosome other than a sex chromosome. In somatic cells there are twenty-two *pairs* of autosomes whereas the sex cells (gametes) contain twenty-two single autosomes.

Genes exist in pairs known as alleles. If the host bears two identical genes for a particular trait such as brown eyes or the Rhesus (Rh) factor, he is known as *homozygous*. If each gene is different (blue eyes and brown eyes or Rh positive and negative) the host is *heterozygous* for that trait.

The genotype is the allelic composition of the host's cells. The phenotype is the expression of the genotype, e.g. eye colour, Rh status, finger length or hair character.

A single gene is thought to determine the synthesis of a single polypeptide chain. Mutation results in the substitution of one amino-acid residue in this chain. Thus the only difference between sickle-cell haemoglobin and normal haemoglobin is that one peptide of the former contains valine instead of glutamic acid.

INHERITANCE

Mendelian inheritance may be one of four types:

1. AUTOSOMAL DOMINANT TRAIT, e.g. achondroplasia, arachnodactyly, Sturge-Weber syndrome, Thomsen's disease and hereditary spherocytosis. An affected heterozygous individual mating with a normal may produce a normal or an affected child in a 1:1 ratio (Fig. 1A). Normal offspring have all normal offspring. Occasionally a generation may be skipped so that an apparently normal person has an affected child. In Fig. 1B it is noted that two affected heterozygotes have offspring in the ratio of 3 affected (1 homozygote and 2 heterozygotes) to 1 normal. A homozygous individual will produce 4 heterozygotes (Fig. 1C).

2. AUTOSOMAL RECESSIVE TRAIT, e.g. Morquio-Brailsford disease, Laurence-Moon-Biedl syndrome, thalassaemia major, retinitis pigmentosa, cystic fibrosis of the pancreas, alkaptonuria, galactosaemia, phenylketonuria and most inborn errors of metabolism. The disease is only recognizable when the gene is present in the homozygous state.

In Fig. 1B the parents are both heterozygous and are apparently normal. They are, however, carriers of the trait, and their offspring include one homozygote who manifests the disease, two heterozygotes who are outwardly normal but *carry* the disease (carrier state) and one entirely normal individual. Recently it has been discovered that the carrier state can sometimes be detected. In Tay-Sach's disease for instance, it can be detected because the enzyme hexosominidase is not normal in carriers as previously thought, but is reduced in quantity.

In Fig. 1A, if one patient is a heterozygote and the other normal, then 50 per cent of the offspring will also be heterozygotes. None manifests the

disease. If as in Fig. 1c one parent is homozygous (affected) then all the offspring will be heterozygous carriers for the abnormal gene.

It can be seen from the above that the recessive homozygous state is uncommon. To produce it *two* carriers must mate, thus the incidence of first cousin marriages is very high in such cases. In the normal population the incidence of cousin marriages is less than 0·4 per cent. Amongst parents who have produced affected offspring for a recessive gene, it may be as high as 35 per cent.

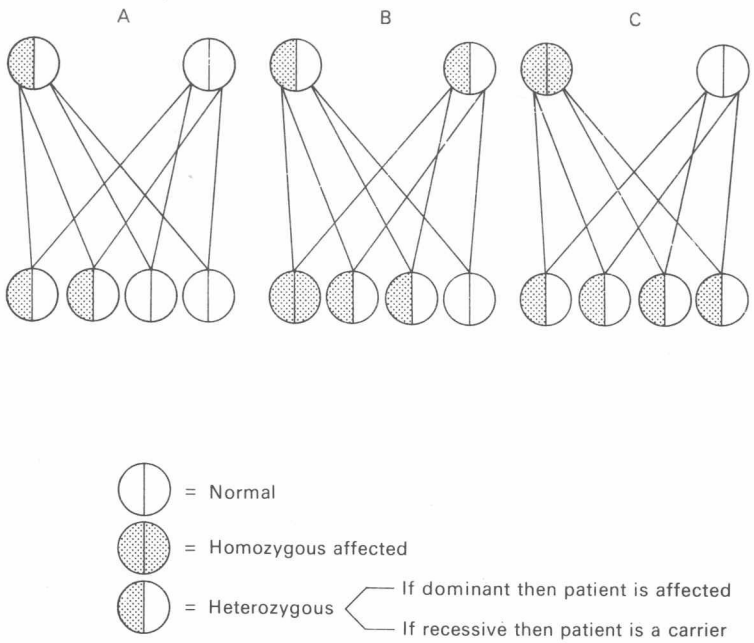

Fig. 1 Autosomal inheritance. In dominant inheritance both homozygotes and heterozygotes manifest the trait. In recessive inheritance only the homozygote manifests the trait. The heterozygote is a carrier and can transmit the trait to its offspring.

3. AUTOSOMAL CO-DOMINANT TRAITS exist when two dominant genes dominate over a recessive gene, e.g. blood group antigens A and B dominate over blood group O.

Gene AA determines the synthesis of normal adult haemoglobin while gene SS determines that for sickle haemoglobin. The heterozygote AS produces equal quantities of A and S haemoglobin.

4. SEX-LINKED TRAITS may be dominant or recessive. The abnormal 'X' will manifest itself in both male and female.

(a) *Dominant sex-linked traits* are transmitted by affected males to their daughters, but not their sons, e.g. glucose-6-phosphate dehydrogenase (G-

6-PD) deficiency and vitamin D resistant rickets due to real phosphaturia (Fig. 2A). The heterozygous *affected* female will transmit the trait to half her sons and half her daughters (Fig. 2B). If an affected male mates with an affected female, three out of four offspring will be affected. One should remember, however, that some of these gene combinations are lethal.

(b) *Recessive sex-linked traits* are transmitted by the female who is a carrier, but the disease is manifested only in the male, e.g. haemophilia

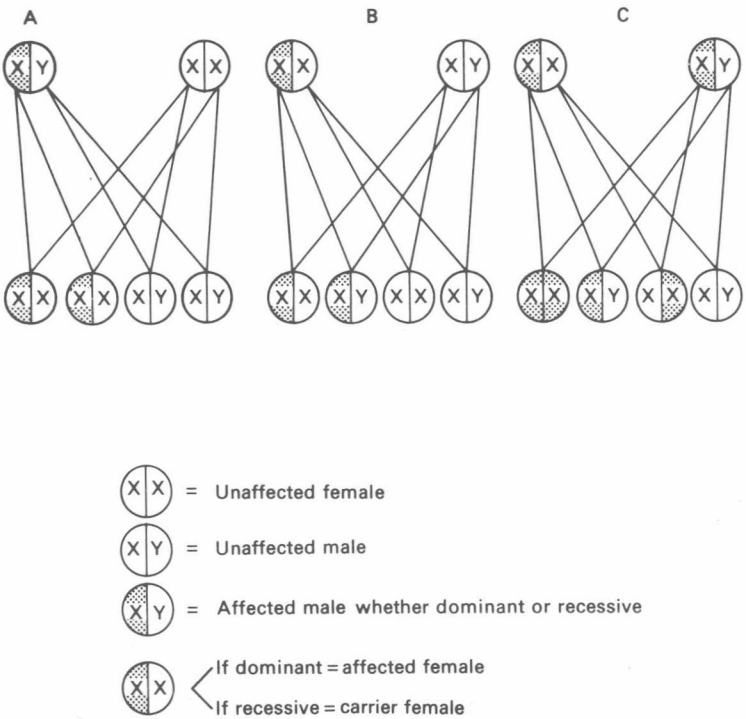

Fig. 2 X-linked inheritance.

(Fig. 2B). It is possible for the female to manifest the disease in the rare circumstance where a male haemophilic mates with a haemophilia carrier (Fig. 2C). The daughter carries two abnormal XXs. It is, however, rare for such a female to survive. In Fig. 2A the haemophilic male produces two carrier females and two normal males.

Nephrogenic diabetes insipidus is a rare congenital defect of water metabolism not responding to pitressin. It is inherited as a recessive sex-linked trait as above. It is found that the heterozygote (carrier) does not concentrate urine as well as the normal person. The offspring of such

carriers should be tested after birth, and those with diabetes insipidus treated.

Many inherited diseases such as diabetes mellitus are multifactorial, i.e. they depend on more than one gene for their expression and are thus not as easy to define as the above diagrams suggest. Furthermore some genetically determined characteristics may be suppressed or brought out by environmental factors (incomplete gene penetrance). Thus sickle-cell anaemia seems to protect the patient against malaria, hence its prevalence in West Africa.

THE CHROMOSOME

Chromosomes are best studied during metaphase. Each is composed of two strands called chromatids attached at the centromere. The following types are described in man, the metacentric, submetacentric and acrocentric (Fig. 3).

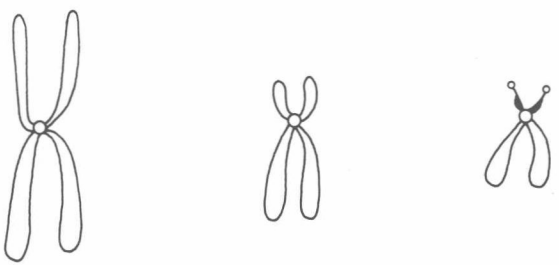

Fig. 3 Chromosomal types (metaphase).

THE HUMAN KARYOTYPE

The karyotype is the arrangement of the human chromosomes into groups. This is demonstrated by photographing them during metaphase, making enlarged photographic prints, cutting out each chromosome and then pairing them. These are placed in seven groups (the Denver Classification). Patou further suggested that each group be labelled in addition with the letters A to G (Fig. 4).

The total number of chromosomes in each body cell is 46 (the diploid number) made up of 22 pairs of chromosomes called *autosomes* and a pair of sex chromosomes designated XX in the female and XY in the male.

The term 'haploid' refers to the number of chromosomes in the sex cells. In man this is 23, which is half the diploid number.

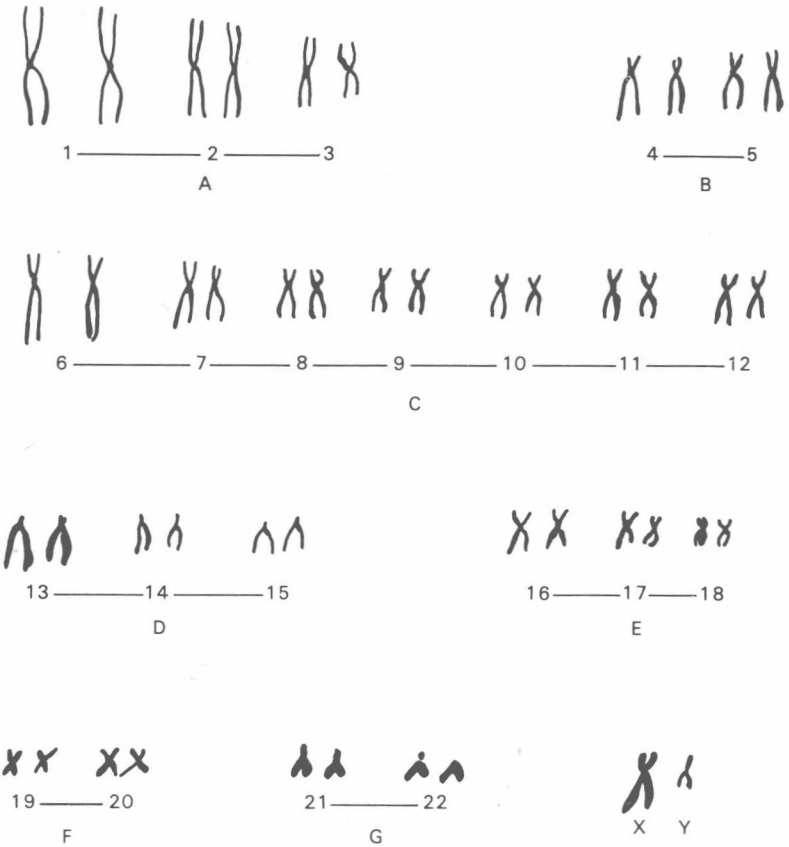

Fig. 4 Normal male karyotype (the female has xx chromosome).

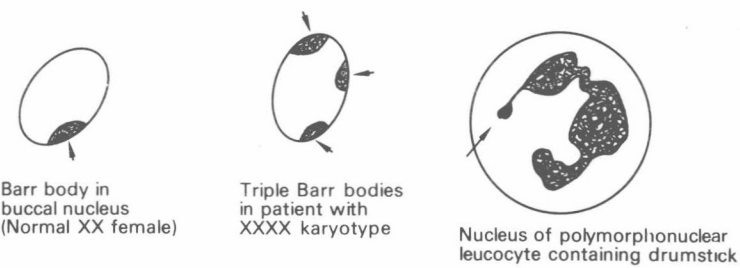

Fig. 5 Sex chromatin.

NUCLEAR SEX CHROMATIN

Barr bodies are chromatin masses 1 μm in diameter, found in the nuclei of females. Cells containing the distinctive mass are called chromatin-positive cells, whereas those without are termed chromatin-negative. Barr bodies occur in 25–60 per cent of interphase nuclei from skin and buccal mucosa of females. A similar body, called a 'drumstick', is found as appendages on 1–3 per cent polymorphonuclear leucocytes in females (Fig. 5).

Barr bodies and drumsticks are thought to represent one of the X chromosomes in the females. It is never seen in normal (XY) males or in Turner's syndrome (XO). In Klinefelter's syndrome (XXY) it is commonly found, because the 'Barr X' is present.

CHROMOSOMAL ABNORMALITIES

It is estimated that 1:250 live-born infants have a chromosomal abnormality sufficient to cause serious physical and mental defects. These abnormalities can all be detected antenatally but it is practically impossible to eliminate these genetic diseases because one cannot predict all the pregnancies which should be screened. One is limited therefore to screening 'high risk' families.

Alterations to the chromosome may be in number or in structure.

1. CHANGES IN NUMBER In Down's syndrome there is an additional homologue on chromosome No. 21 hence the name Trisomy-21. It is probably due to non-disjunction, i.e. the failure of the homologous chromosome to go to opposite poles during meiosis (Fig. 6). Increasing age is a factor in non-disjunction. Trisomy-18 and trisomy-13 also have been documented, but are very rare.

Loss of a chromosome (monosomy) occurs in Turner's syndrome, where an X chromosome is absent, while Klinefelter's syndrome exhibits an extra X due to non-disjunction of the X-chromosome.

Mosaicism is an anomaly of chromosome division resulting in cells containing different numbers of chromosomes (chimaerism).

Aneuploidy is a deviation from the normal diploid number of 46. An increase may be triploid (69 chromosomes per cell) or tetrapoloid (92

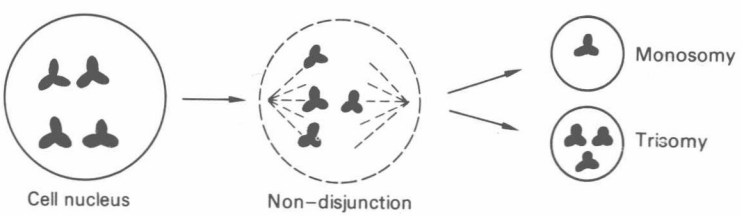

Fig. 6 Non-disjunction leading to trisomy and monosomy.

chromosomes per cell). A decrease in the diploid number is called hypodiploidy.

2. STRUCTURAL CHANGES Translocation (the commonest structural change) is the exchange of genetic material between any two chromosomes. Usually the chromosome number of 46 is maintained but in the type of translocation known as 'centric fusion' one chromosome is lost. Down's syndrome in young mothers is commonly due to translocation. The commoner form of this disorder, which is associated with elderly parents, is due to trisomy-21 (see Fig. 6).

Partial deletion of chromosome No. 5 occurs in 'cat-cry syndrome'. Ring forms occur when both ends of a chromosome are lost.

Many alterations in structure or number are incompatible with life, and are detected in aborted foetuses.

It should be recognized that 1 in 1000 persons has a chromosomal rearrangement which does not produce obvious clinical effects because there is no loss or gain of genetic material. They are known as *balanced translocation carriers*. They are, however, liable to produce abnormal gametes and hence abnormal offspring. In fact they are usually only detected after they have produced an abnormal infant, e.g. a baby with Down's syndrome. For subsequent children, such parents can be offered prenatal diagnosis and selective abortion in countries where this is permitted.

PRENATAL DIAGNOSIS

By the 14th–16th week of pregnancy it is possible to obtain 10–20 ml amniotic fluid by means of suprapubic puncture of the uterine cavity. The fluid is examined for biochemical abnormalities while the cells, which are foetal in origin, are cultured and examined for both biochemical and chromosomal abnormalities. The risk to both mother and foetus seems negligible in skilled hands.

For the present these techniques are limited to a few large centres and the following are some of the disorders which have yielded to antenatal diagnosis:

A. METABOLIC DISEASES

1. Tay-Sach's disease (amaurotic family idiocy).
2. Duchenne muscular dystrophy.
3. Gaucher's disease.
4. Glycogen storage disease and galactosaemia.
5. Maple syrup urine disease.

B. CHROMOSOMAL DISORDERS

The most notable is Down's syndrome (mongolism). It is stated that 1 in 70 pregnancies in women over the age of 40 and 1 in 40 over the age of 45 result in a mongol.