

Progress in
CLINICAL MEDICINE

EDITED BY

A. R. HORLER

J. B. FOSTER

SEVENTH EDITION

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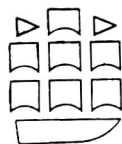
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CHURCHILL LIVINGSTONE

EDINBURGH LONDON AND NEW YORK 1978



CHURCHILL LIVINGSTONE
Medical Division of Longman Group Limited

Distributed in the United States of America by
Longman Inc., 19 West 44th Street, New York,
N.Y. 10036, and by associated companies,
branches and representatives throughout
the world.

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the publishers (Churchill Livingstone,
23 Ravelston Terrace, Edinburgh EH4 3TL)

First edition 1948
Reprinted 1948
Second edition 1952
Third edition 1956
Fourth edition 1961
Reprinted 1963
Fifth edition 1966
Reprinted 1967
Sixth edition 1971
Seventh edition 1978

The sixth edition was edited by Raymond Daley and
Henry Miller

ISBN 0 443 01697 6 (Cased)
0 443 01421 3 (Limp)

British Library Cataloging in Publication Data

Progress in clinical medicine. - 7th ed.

1. Pathology 2. Medicine, Clinical

I. Horler, A R II. Foster, John Barnes
616 RB111 77-30227

Printed in Great Britain by Adlard & Son Ltd, Bartholomew Press, Dorking

Preface

Progress In Clinical Medicine first appeared in 1948 under the joint editorship of Drs Raymond Daley and Henry Miller. Their intention was to produce an up-to-date account of the advance of medical knowledge that would be of particular value to the general physician in active clinical practice, and to the postgraduate student seeking higher qualifications. For this they recruited a formidable team of contributors representing each of the recognised medical specialties in addition to their own. The success of this venture was evinced by the regular production of further editions, each entirely rewritten, ending with the sixth in 1972. The introduction of fresh subjects of topical interest with their appropriate author, ensured that the book retained its interest and vitality and continued to fulfil its original purpose.

On their relinquishing the editorship after the sixth edition, we undertook the task of producing its successor, fully conscious of the standard that had been set. We have endeavoured to maintain the balance and design of the book and to invite contributors from various representative medical centres. Inevitably the reader will discover some overlap between certain chapters as each author deals with material relevant to his own subject. This only serves to underline the interdependence of the various specialties that constitute clinical medicine.

We are very grateful for the invaluable assistance we have received from Mrs Heather Russell, both in script-reading and in preparation of the index. We are also grateful to several authors and their publishers for permission to reproduce certain figures and tables, acknowledgement for which appears in the text.

We could not complete this introduction without expressing our deep regret at the recent death of Henry Miller and our disappointment that he did not see this latest edition on the bookshelves. Much has already been written of his contribution to clinical medicine and neurology but we should like to pay particular tribute to him and his friend and colleague, Raymond Daley, for the inspiration that gave birth to *Progress in Clinical Medicine*.

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1. Genetics

Sir Cyril A. Clarke

A Chromosomes in Medicine

It would be idle to pretend that chromosomal abnormalities account for more than a fraction of human pathology, and it is unnecessary for a clinician to be acquainted with every newly published set of marionettes. Nevertheless, chromosomes are coming much closer to ordinary medicine and some knowledge of them is desirable—the information is basic and in a few cases can be most helpful in accurate diagnosis and prognosis.

Before discussing the clinical aspects of the discipline it is important to learn (or relearn) some of the terminology.

DEFINITION OF TERMS

Karyotype. This is the term used to mean the whole chromosomal picture of *somatic* cells and normally, no matter what organ is examined, there are 22 pairs of autosomes and one pair of sex chromosomes, X and Y in the male and X and X in the female. It is important to remember that genes only exert their effect in appropriate tissues; for example, the sex chromosomes are inert as regards sex, except in the cells of the reproductive organs where they become responsible for the differentiation of the gonads.

Mitosis. This is the process which occurs when somatic nuclei divide. Each chromosome duplicates (*syn. replicates*) itself, so that two chromatids are formed; one of these passes to one pole of the nucleus and the other to the opposite one. The nucleus and the cell then also divide and form two new daughter cells, each of which carries an exactly similar complement of genes to the mother cell. The other features to be remembered about mitosis are: (1) that the homologous chromosomes do not pair (*cf. meiosis*) and (2) that the chromatids are held together for a short time by the centromere and it is then that further division can be halted by colchicine and the chromosomes examined and photographed (see Fig. 1.1). The position of the centromere is constant for any given chromosome and is normally situated anywhere except at the extreme end.

Meiosis. This type of division occurs only in the testes and ovaries, the process taking place in many precursors of the spermatozoa (spermatocytes) simultaneously but only in one oöcyte at a time. Though there are many steps in meiosis there are only two essentials to remember: (i) in each ovum and spermatozoon the chromosome number is halved, so that it becomes haploid instead of diploid; (ii) genetic interchange (crossing-over or recombination) occurs at the stage when the homologous chromosomes (one of which is paternal and one maternal) pair, which they do before they separate.

Crossing-over or recombination. This is very important because it ensures the genetic

variability on which natural selection depends. However, it is still uncertain as to precisely what happens during the process. Most descriptions suggest that the exchange of genetic material is brought about by breakage and rejoining of parts of the two chromatids. However, the old explanation of Belling (1933) is more in keeping with the chemistry of DNA. He suggested that the duplication of the chromosomes takes place irregularly so that the connecting fibres join up groups of genes from both paternal and maternal chromatids. Figure 1.2 explains this in more detail.

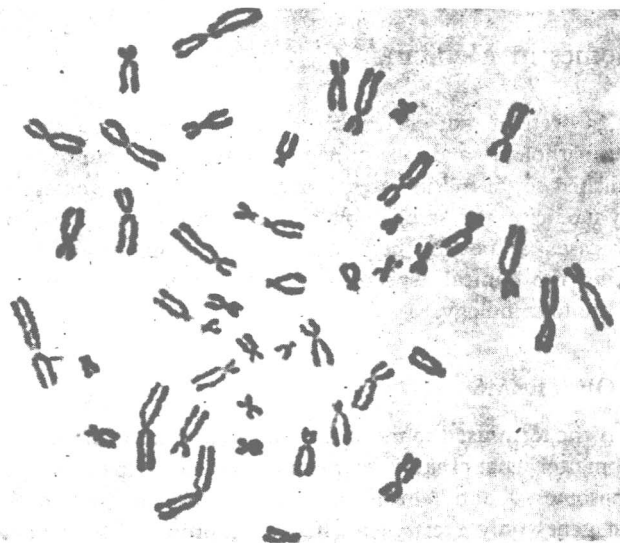


Fig. 1.1 This shows the 46 chromosomes from a single somatic male cell undergoing mitosis. The chromosomes have doubled but are still held together by their centromeres. Those chromosomes where the centromere is in the middle are called metacentric and those where it is near the end, acrocentric. (From C. A. Clarke, 1964, *Genetics for the Clinician*, by courtesy of Dr S. Walker and Blackwell Scientific Publications.)

Non-disjunction. If a pair of homologous autosomes or the sex chromosomes stay together instead of separating at meiosis, non-disjunction is said to have occurred. The resulting spermatozoon or ovum then receives either *two* of the particular chromosome involved or *none*, though in all other respects the gamete will have the normal chromosome complement. On fertilisation with a normal gamete, the zygote will either be trisomic or monosomic for the particular pair of chromosomes in which non-disjunction has occurred. Non-disjunction can also occur at mitosis, after which mosaicism (q.v.) results. Mongolism is usually due to trisomy of chromosome 21, and Klinefelter's syndrome (XXY) and some forms of Turner's syndrome (XO) are examples of trisomy and monosomy respectively involving the sex chromosomes (see German (1970) for a good review of Turner's syndrome).

Isochromosome. The simplest way to understand this is to take a specific instance; for example, Turner's syndrome. Most women who suffer from this are chromosomally XO, but sometimes they are XX, and in this case one of the Xs is often abnormal (an isochromosome). This is produced as follows: normally the X chromosome divides longi-

tudinally (down the middle) so that each daughter cell receives both the long and the short arms of the chromosome with all their genes. If the X chromosome divides *across* (see Fig. 1.3) there results either an isochromosome made up of two long arms of the X, which will contain two sets of the genes on the long arm but none of those on the short, or vice versa (see Priest et al, 1975, for review of X-isochromosomes). Isochromosomes are also probably formed, though rarely, as a result of abnormal division of the autosomes.

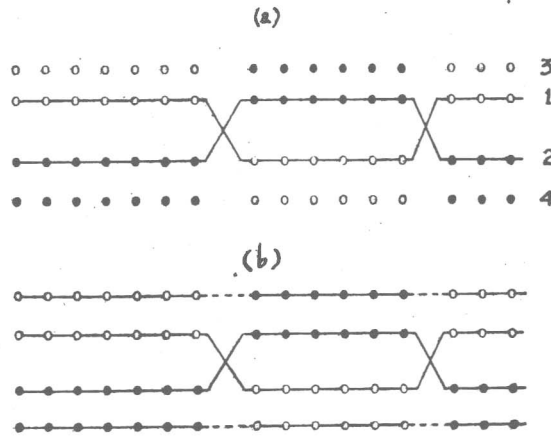


Fig. 1.2 The diagram shows how the duplication of chromosomes and crossing-over may take place at meiosis. In (a) two chromosomes (1, 2) are shown wound round each other and replication has taken place (3, 4). In (b) the new connecting fibres have joined up replicated groups of genes from *both* chromosomes so that the new chromatids, instead of being exact copies of the old, contain some maternal and some paternal genes (Belling, 1933).

Barr body. This is a densely staining body just inside the nuclear membrane which is present in the somatic cells of females (who are said to be **chromatin positive**) but only rarely in males (**chromatin negative**), and it is usually tested for in cells from a buccal smear (see Fig. 1.4). It represents the inactive X chromosome (see Lyon hypothesis, p. 17).

Another structure which helps to distinguish the sexes cytologically is the drumstick appendage (see Fig. 1.5) which is found in about 3 per cent of the neutrophil leucocytes of females, but is absent in males. The incidence of the trait is influenced by the degree of lobing of the nucleus, the more highly lobed cells having a greater incidence of drumsticks (Mittwoch, 1975).

Translocation. In a translocation two non-homologous chromosomes have joined together (a small piece from each being lost in the process). As a result, when the chromosomes are arranged in pairs, it is found that one each of two different pairs, e.g. one of the number 13s and one of the number 15s is missing, and in their place is an abnormally large chromosome. The important thing to remember when this happens is that the total amount of chromatin remains normal (or nearly so); the individuals concerned are therefore unaffected and are known as translocation carriers. It is in the succeeding generation that abnormalities may occur. A Robertsonian translocation is one where the break has occurred near the centromeres in two acrocentric chromosomes. The result of fusion is

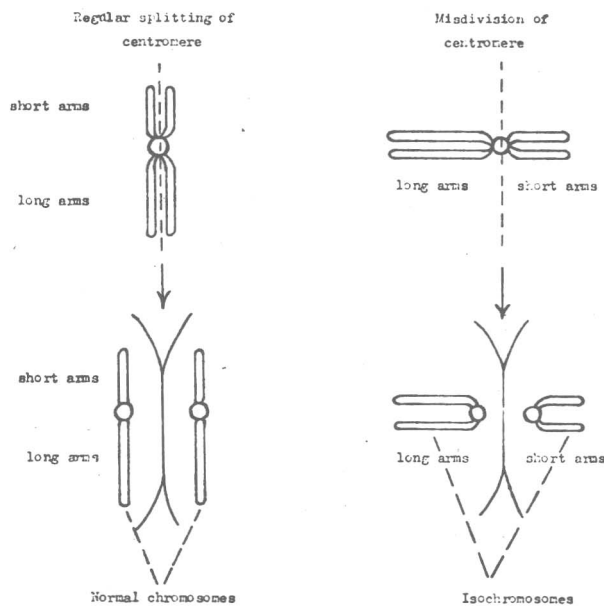


Fig. 1.3 The origin of an isochromosome through misdivision of the centromere during mitotic division. (From J. L. Hamerton, 1962, *Chromosomes in Medicine*, by courtesy of Dr W. G. Harnden and Messrs Heinemann.)

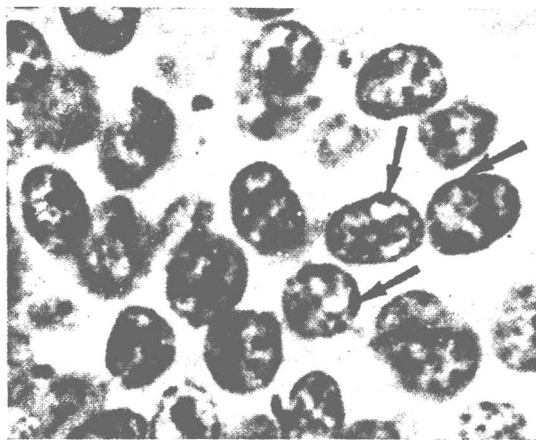


Fig. 1.4 Epithelial cells from the buccal mucosa of a female patient showing Barr bodies in the nuclei ('chromatin positive'). (By courtesy of the late Dr Winston Evans, David Lewis Northern Hospital, Liverpool.)

one metacentric chromosome and a fragment, which is often lost. Robertsonian translocation is thought to have been an important mechanism in the evolution of metacentric chromosomes from acrocentric ones.

Deletion. A deficiency of part of a chromosome. The small abnormal chromosome (Ph_1) often present in myeloid leukaemia is the result of a deletion, probably in chromosome 21.

The *cri du chat* syndrome (see p. 22) is caused by a deletion of part of a chromosome no. 5.

Mosaicism. Individuals who are mosaics have tissues some of which are of one chromosomal constitution and some of another; for example, a proportion of patients with Turner's syndrome are XO/XX mosaics. The condition results either from non-disjunction (q.v.) occurring at mitosis or because of *anaphase lag*, where a chromosome gets lost at the stage during which the duplicated chromosomes pull apart just before the separation into two daughter cells. Mosaicism can be detected by chromosome culture,

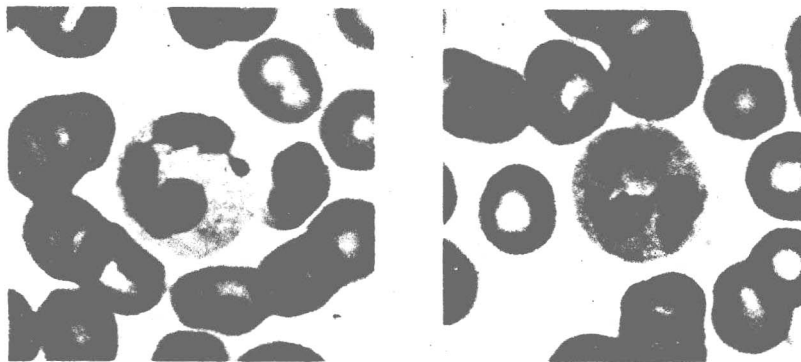


Fig. 1.5 *Left:* Neutrophil leucocyte, a drumstick nuclear appendage, in a blood film from a normal female. Giemsa stain, $\times 1800$. *Right:* A neutrophil leucocyte from a normal male, in which cells with drumstick appendages are lacking. This cell would, equally well, illustrate over 90 per cent of neutrophils of females. Giemsa stain, $\times 1800$.

but it is also potentially recognisable clinically, e.g. if a Turner patient were colour-blind in one eye and not in the other. Mongol mosaicism, e.g. 46/47, is being increasingly recognised (see p. 20). A mosaic differs from a *chimaera* in that a mosaic is formed of the cells of a single zygote lineage while a chimaera has cells which derive from two or more distinct zygote lineages.

Locus. This is the site on a chromosome occupied by a particular gene or a member of a particular allelomorph series.

Linkage. Genes, or more accurately the loci they occupy, which are situated on the same chromosome are said to be linked and are inherited together, except when crossing-over occurs. The loci for the nail-patella syndrome and for the ABO blood group alleles are an example of this in man. The closer together the genes, the less likely is crossing-over to occur, and some genes are so close together that they have never been observed to become separated. Those comprising the Rh blood group complex, for instance, are inherited as a unit, though there must have been occasional crossing-over *within* the complex (which is an example of a supergene) in order to give rise to some of the rarer Rh genotypes.

Linkage disequilibrium. Combinations of alleles of linked genes which have frequencies

significantly different from those expected with random combination—a situation found, for example, in mimicry in butterflies, when genes are ‘cooperating’ to perfect a particular pattern.

Association. In medical genetics, this means that an allele occurs more frequently than would be expected by chance in patients suffering from a particular disease. For example, there is a striking association between HLA group W27 and ankylosing spondylitis. Sometimes association is difficult to distinguish from linkage.

Phenocopy. An exact replica of an inherited character, but produced environmentally. The deaf-mutism in the offspring of mothers who have had rubella in the first three months of pregnancy is indistinguishable from the inherited type.

DESOXYRIBONUCLEIC ACID (DNA)

Chromosomes are composed of desoxyribonucleic acid (DNA) and a molecule of this consists of two chains, each made up of a desoxyribose phosphate backbone and a series of purine and pyrimidine bases which pair with those on the opposite chain. The molecule is constructed like a double spiral staircase of which the phosphate backbones form the ‘banisters’ and the nitrogenous bases the ‘steps’. The pyrimidine bases forming these ‘steps’ are cytosine and thymine, and the purines adenine and guanine. Thymine normally pairs with adenine (mnemonic ‘t s and a s’) and guanine with cytosine (mnemonic ‘Gc’). Figures 1.6 and 1.7 illustrate these points. A single molecule of DNA may have as many as 10000 purine–pyrimidine pairs and its molecular weight is about 6000000. The original paper on the structure of DNA (Watson and Crick, 1953) is readily comprehensible to any physician and no later work has contradicted it.

Replication

It is worth considering how the replication of DNA is effected. It is probable that its two chains, which are wound round each other, separate and then each single chain will have a series of bases needing new partners. These are taken from the nucleotide pool and the appropriate freshly synthesised nucleotide bonds itself to the right base on the old chain, guanine plus its sugar and phosphate if, for example, cytosine is needing a new partner, adenine plus its sugar and phosphate if thymine is needing one. This mode of replication is called ‘semi-conservative’ since each new double chain consists of one old and one new chain and is consistent with the Belling hypothesis of the events occurring at meiosis (see Fig. 1.2).

Supporting evidence that this hypothesis of replication is correct came from the work of Meselson and Stahl (1958). These workers grew *Escherichia coli* for many generations in a medium of which the nitrogen consisted entirely of the radioactive isotope ^{15}N . Eventually, therefore, this constituent of the DNA molecule was all in the labelled and readily identifiable form. The bacteria were then transferred to a medium where the nitrogen was of the ordinary form (^{14}N), and after one generation all the molecules were found to be hybrid, containing equal amounts of ^{14}N and ^{15}N . In the next generation the number of hybrid molecules remained the same, but an equal number of pure ^{14}N molecules had appeared, and these continued to increase in subsequent generations.

DNA has now been synthesised in vitro. Goulian, Kornberg and Sinsheimer (1967)

put the DNA of a pigmy virus (Phi X174), labelled with tritium, in a test-tube together with the bases adenine, guanine, cytosine, and, instead of thymine, bromouracil. The addition of the enzyme polymerase caused a circle of artificial DNA to be formed from the bases around that of the natural DNA. The two circles could be separated, because bromouracil is heavier than thymine. This artificial DNA was found to be able to repro-

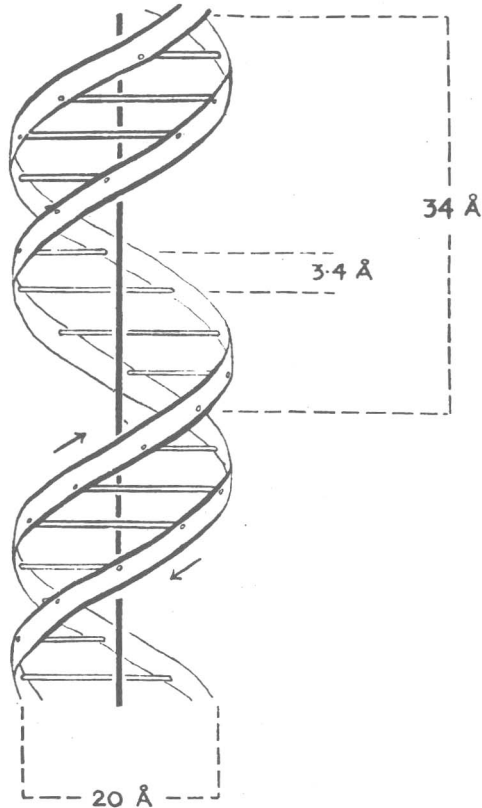


Fig. 1.6 Diagram representing the double spiral 'staircase' of the DNA molecule, giving dimensions in Angstrom (one hundred millionth of a centimetre) units. The outer bands represent the phosphate-sugar chains and the horizontal rods the paths of the bases holding the chains together. The arrows indicate that the sequence of bases goes one way in one chain and the opposite way in the other. The vertical line represents the axis of the molecule.

duce itself just as if it were natural DNA, and so, moreover, was a second generation artificial DNA which these workers formed from their first artificial DNA. This work led to the idea of genetic engineering, meaning that it might be possible to attach a particular gene to harmless viral DNA and use this virus as a vehicle for delivering the gene to the cells of a patient who has an hereditary defect. On the other hand, this type of experimental approach might be dangerous, for some viruses are oncogenic, and in error they might become incorporated into a common bacterium such as *E. coli* and thus spread through a human population. A moratorium on this type of research was therefore proposed by the US National Academy, but the committee set up in this country,

chaired by Lord Ashby, thought that with due precautions such experiments could continue.

The genetic code

The vital importance of DNA is that it can initiate the transmission of information to the amino acids in the cytoplasm so that they can form correct polypeptide sequences

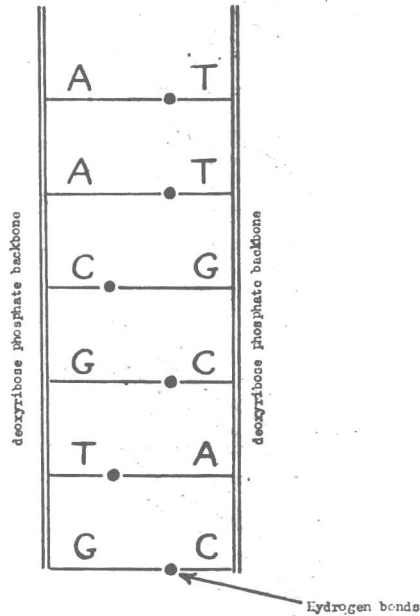


Fig. 1.7 Diagram showing the way in which the nitrogenous bases of DNA are paired, facing inwards from the phosphate-sugar chain and joined together by hydrogen bonds.

and hence the right proteins. For example,

G-C
C-G
A-T

would carry a different message from that of:

A-T
G-C
T-A

Although the information arises in the DNA of the nucleus, the proteins are manufactured in small particles in the cytoplasm called ribosomes. An intermediate step is to transmit the information to the ribosomes by 'messenger' RNA, which is similar to DNA but has only one chain. It is also slightly different in constitution, having uracil instead of thymine, and presumably when the DNA 'says' adenine-thymine, the RNA (having

only one chain) translates this into adenine-uracil. Transcriptase is the enzyme responsible for making RNA out of DNA.

THE DECIPHERING OF THE GENETIC CODE

It is known experimentally that a sequence of uracil in the RNA ensures that a chain of the amino acid phenylalanine results, whereas a cytosine sequence produces proline, but how many bases form the code word determining one specific amino acid sequence? Crick et al (1961) have shown that (for bacteriophage anyway) the answer is *three*, and the reasoning for this is as follows:

First, if the coding were of four bases there would only be 16 combinations (4×4) which would not be enough to code the 20 or more essential amino acids. However, using three of the four bases there are 64 ($4 \times 4 \times 4$) different groupings which is more than adequate and it seems probable that more than one triplet codes the same amino acid. Second, Crick and his colleagues (1961) have performed some critical experiments with the bacteriophage, T4. This phage will normally grow on two different strains of *E. coli* but when a mutation consisting of the addition of a purine or pyrimidine base takes place in the DNA of the phage, it puts wrong the coding which follows the mutation, and then the phage is only able to grow on one of the strains of the bacterium. When, however, a second mutation consisting of a deletion of a base takes place close to the first one, the original order is restored in subsequent bases and the phage will then grow on both strains of *E. coli*. This could occur, however, if many bases formed the codeword, but the triplet hypothesis is shown to be true by the fact that two more additions besides the first one—that is three additional bases in all—will restore the subsequent bases to their original and correct order. This would only be the case if the code consisted of a word of three or a multiple of three letters.

That the three bases are only read once and that the code does not overlap is proved by the fact that a mutation in the sense of alteration (not deletion or addition) of a base only alters one amino acid. It does *not* alter the amino acids controlled by the 'words' on each side of the mutated 'word'.

It is probable that what happens in bacteriophage is applicable to man. In sickle-cell haemoglobin, for example, the single substitution of the amino acid valine for glutamic acid is sufficient to change Hb A to Hb S, and this could be explained by a mistake in the pairing of the DNA bases. Thus if adenine were temporarily to occur as its isomer at the moment of replication, it might pair with cytosine instead of thymine. At the next replication, however, adenine, having reverted to its usual form, would pair normally with thymine and cytosine with guanine. There would, however, have been one change in the sequence of bases and this would be reproduced indefinitely.

Reverse transcriptase. Sometimes a virus, for example the one responsible for mammary cancer in mice, possesses an enzyme, reverse transcriptase, which enables it to make DNA from RNA. A similar virus has been found in human milk, and reverse transcriptase is also present in RNA molecules in human breast cancer cells. The implication is that these RNA molecules appear in the cancer cells because there is a human milk virus containing reverse transcriptase replicating in them.

It must be emphasised that what has been discussed is at the molecular level, whereas what follows mainly concerns structures visible under the microscope.

TECHNIQUES AND NOMENCLATURE

Chromosomes can only be seen in actively dividing cells, and it is therefore usually bone marrow, peripheral blood and skin which are investigated.

Bone marrow. This is most often looked at in cases of leukaemia and therefore the cells are examined without culture in order to obviate normal cells overgrowing the leukaemic ones. A few drops of marrow only are necessary.

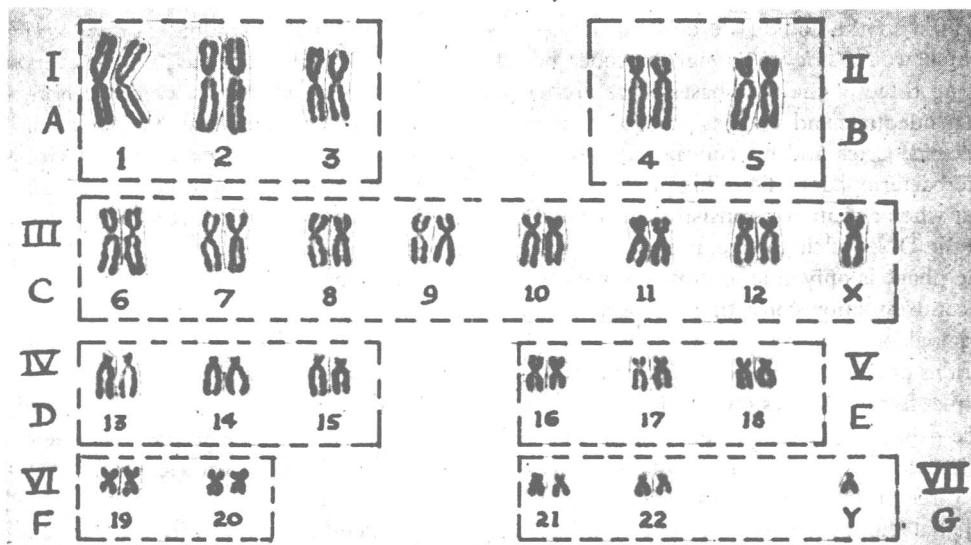


Fig. 1.8 This shows the same 46 doubled chromosomes as in Figure 1.1. The autosomes are arranged in decreasing order of size and numbered from 1 to 22. The X and Y are not numbered. The seven groups of the Denver and Patau classifications are indicated by the Roman numerals and appropriate letters. These are still used even though each human chromosome can now be identified by Giemsa staining, but this technique is not yet in general use. (From C. A. Clarke, 1964, *Genetics for the Clinician*, by courtesy of Dr S. Walker and Blackwell Scientific Publications.)

Peripheral blood. An ideal volume is 5 ml of venous blood, and this is readily obtainable from an adult. However, it is a large amount to take from a child (though experts can get it either from the jugular vein or fontanelle), and it is now possible to make preparations from a few large drops of capillary blood obtained by finger prick or heel stab. In these microtechniques whole blood is studied, whereas in adults the leucocytes are isolated. Phytohaemagglutinin is then added, and this stimulates the leucocytes to divide after they have been cultured under sterile conditions at 37°C for about three days. Colchicine is next introduced because it stops mitosis at the time when the chromosomes are most contracted and easily defined. The addition of hypotonic saline to swell the cells makes it easier to count them accurately. Nevertheless, many cells from one culture must be examined because chromosome breakages and artefacts lead to difficulties. The chromosomes are next photographed so that individual ones can be cut out and arranged in pairs, as shown in Figure 1.8.