Biochemical Frontiers in Medicine

BY FIVE AUTHORS

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preface

The human body is a complex chemical system in which many thousands of types of metabolic reactions proceed under elegant controls. These controls vary throughout the life of the individual, but from conception to death they and the reaction systems controlled by them are the "read-outs" of genetic codes that may be characterized not only by the special information that they possess but also by the "biological clocks" that they contain.

It is now recognized that many diseases result from aberrations of these genetic codes and, moreover, that the biochemical machinery of the body has a wide variety of weaknesses which, with present knowledge, cannot be fully delineated.

Since the days of Virchow, when the vast bulk of fundamental pathology was recognized, efforts of medical scientists have been directed toward the elucidation of pathogenetic mechanisms as well as rational therapy. At the present time much progress has been made, although it is clear that our knowledge in these complex fields is actually in a very primitive state.

Biochemical Frontiers in Medicine was designed to provide basic information on subjects in biochemistry that have assumed, or are developing, importance in clinical medicine. It was recognized from the outset that progress in this field, rather than complete details, would be reported, inasmuch as a number of these fields are in flux. An effort has been made to include in this volume areas of interest to medical students,

general practitioners, and specialists in a variety of fields who might need to be brought up to date on biochemical topics in their own fields of special interest and in other related ones. Since many medical students ask the question of the relevance of biochemistry to clinical medicine, it seems important that subjects of interest to them and the medical faculties should also be included.

It is apparent that this volume is not all inclusive. The authors hope that future volumes will cover topics that cannot be presented here and will thereby broaden the area of coverage in medical biochemistry as a whole.

Harris Busch

Houston

contents

Biochemical Frontiers in Medicine

chapter 1

biochemical basis of genetic aberrations

HARRIS BUSCH

All that we are and all that we can be is predestined in part by our genetic potential. Those characteristics by virtue of which we are different from one another are few in number by comparison with the large number of similarities of man to man, regardless of race. The millions of genetic factors that define the size, shape, and organization of the human body are only now beginning to reach the stage of comprehensibility. It will likely be a long time before disease states will be completely definable in biochemical or molecular terms, but the great progress being made supports the view that our understanding of the biochemical pathology underlying many diseases may advance to the point where individual diseases will be completely understood and, more important, new forms of therapy will be developed that may be more specific than existing methods and procedures.

The vast effort in progress today to define disease in molecular or biochemical terms has been extended to the

genetic factors responsible for the existence of abnormal molecular species. The growing list of diseases of proven genetic origin (Table I) has heightened the interest in the genetic apparatus and its abnormalities. If we are to realize the hope that our approach to patient care will be improved as our understanding of biochemical pathology increases, it is logical that we should attempt to comprehend the mechanisms underlying the development of the biochemical abnormalities. Since life, development, and susceptibility to disease in the individual begin with fertilization of the egg and each subsequent step of division of the daughter cells, it behooves us to comprehend not only phenotypic development of the individual but also the development of the genotype that is established in the zygote. The purpose of this chapter is to indicate our present understanding of the constituents of the apparatus for transmission of genetic information and to provide some information on the operation of the system in terms of cellular phenotypes and to relate these to the biochemical characteristics of some molecular diseases.

the chromosomes

The biologic unit of the genetic apparatus is the chromosome, that structure presumably composed of the genes and supporting structures. Enormous advances have been made in the technology for visualization and description of the structures, numbers, and types of chromosomes of man. In the last ten years improvements have been made that have revolutionized this field, of which three in particular stand out. The first of these is the use of hypotonic media to swell cell nuclei and to provide separation of the chromosomes. Older methods of visualizing chromosomes suffered from the fact that the chromosomes overlapped one another and were crowded together; moreover, the crowding bent the chromosomes over one another and distorted their shapes. A second improved method of visualizing the chromosomes is the squash technique, in which forceful pressure of the thumb on the cover slip of the slide is used to flatten the nuclei of the cells and the chromosomes. Finally, a most helpful step is the use of stathmokinetic or cytostatic agents such as colchi-

Table I

Genetically transmitted diseases

Chromosomal diseases
- Mongolism
- Polydys-spondylism
- Klinefelter's syndrom
- Turner's syndrome
- Superfemale
- Leukemia, especially chronic myelogenous leukemia
- Anencephaly
- Epiloia
- Laurence-Moon-Biedl syndrome
- Neurofibromatosis
- Arachnodactyly
- Osteogenesis imperfecta
- Achondroplasia
- Micro-orchidism

Abnormalities of blood proteins
- Haptoglobinemia
- Abnormal serum transferrins
- Abnormal gamma globulins
- Agammaglobulinemia
- Double albumins
- Low serum pseudocholinesterases
- Low glucose-6-phosphatase
- Low isoniazid "inactivators"
- Abnormal hemoglobins:
  - Hemoglobin S
  - Hemoglobin E
  - Hemoglobin C
  - Hemoglobin G
  - Hemoglobin M, M_M, M_S
- Analbuminemia
- Thalassemia major
- Afibrinogenemia
- Acatalasemia
- Galactosemia

Abnormalities of urinary products
- "Maple syrup urine"
- Hypoglycemia due to leucine sensitivity
- L-arginosuccinicaciduria
- Cystathioninuria
- Fructosuria
- Nephrogenic diabetes insipidus
- Renal glycosuria
- Cystinuria (osis)
- Phosphaturia (resistant rickets)
- de Toni-Fanconi syndrome
- Hartnup's disease
- Glycinuria
- Hyperoxaluria
- Phenylketonuria

Storage diseases
- Glycogen storage:
  - Low glucose-6-phosphatase
  - Low debranching enzyme
  - Low branching enzyme
  - Low phosphorylase
- Lipogranulomatosis
- Idiopathic hemochromatosis
- Increased plasma lipids
- Hyperkalemic familial periodic paralysis
- Wilson's disease
- Tay-Sach's disease

Others
- Hypophosphatasia
- Gout
- Cystic fibrosis of the pancreas
- Congenital nonhemolytic jaundice

cine and vinblastine to block division of the cells in the metaphase stage of mitosis. This last procedure provides the opportunity to observe the chromosomes of a much larger number of cells than was possible previously.

With the aid of these new methods, it is now possible to define the idiogram or karyotype of individuals and species with relative ease (Figures 1 and 2). The idiogram is simply a representation of the chromosomes of the individual or the species in order of decreasing size and complexity.

Studies of the type shown in Figures 1 and 2 were initially made from testicular preparations obtained from executed prisoners, but such materials had the disadvantage that postmortem decay produced many artifacts. Over a long period studies were made only with tissue culture cells, which provided much more controlled conditions. Such cells as leukocytes and cells of the bone marrow grow readily in tissue culture. More recently, patients have been pretreated with colchicine prior to biopsy of the marrow and satisfactory preparations have also been obtained.

It can now be stated that the normal karyotype for man consists of 23 chromosome pairs, or 46 chromosomes, of which three pairs (Figure 3) can be grouped as large-median chromosomes, two pairs as large-submedian, seven pairs as medium-submedian, three pairs as medium-acrocentric, three pairs as rather short-median or submedian, two pairs as short-median, and two pairs as very short-acrocentric. The X-chromosome is a medium-submedian chromosome and the Y-chromosome is a very short-acrocentric chromosome.

The substructures of the chromosomes that are most readily visible are the kinetochore, or the primary constriction by which the chromosome attaches to the mitotic spindle, and the arms. The arms determine its classification as large, medium, rather short, short, and very short. The kinetochore may be at the center of the chromosome, near one end, or part way between the center and one end. If it is near one end the chromosome is called acrocentric, and if it is at the center its position is median (or metacentric). If the kinetochore is between the end and the center it is submetacentric. In the idiogram, the positions of individual chromosomes within the group are defined in order of diminishing size.

structural abnormalities of chromosomes

It would seem logical that if there were an abnormality of so large a segment of the genetic apparatus as the chromosome, surely there would be serious consequences in the affected individual. A list of the diseases related to abnormalities of the chromosomes appears in Table I, although it should be frankly stated that this list is by no means com-

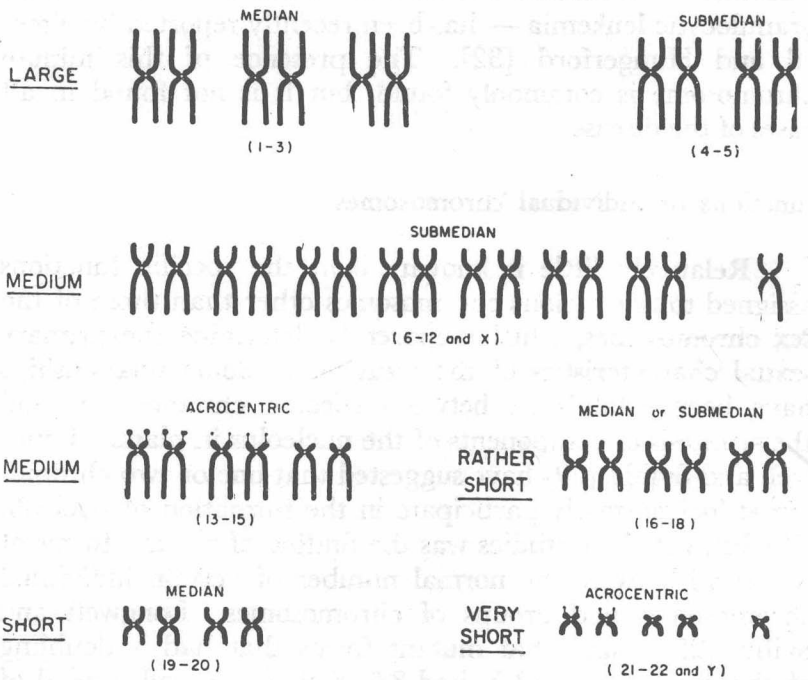

Figure 3. Idiogram of normal human male with 22 pairs of autosomes. The X and Y sex chromosomes are separated from the autosomal pairs. The chromosomes are arranged according to their height primarily and also according to the position of the centromere. From Sohval [40].

plete at this time. It is no particular surprise that individuals with abnormal numbers or types of sex chromosomes manifest abnormalities of sex development. Thus, patients with Klinefelter's syndrome have functional impairment of the testis and patients with Turner's syndrome have abnormally small or no gonads and lack female genitalia or secondary

sex characteristics. The function of the extra small chromosome of the type of pair 21 (the trisomic) of the Mongolian idiot is quite intriguing. In this case, there is no basis for prediction of the abnormality of maturation or intelligence that accompanies the disease. Whether this abnormal chromosome exerts a blocking effect on activities of other chromosomes or whether it is responsible for production of substances that impair cerebral growth or function remains to be determined. Another interesting abnormality of the chromosomes — a minute chromosome associated with human granulocytic leukemia — has been recently reported by Nowell and Hungerford [32]. The presence of this minute chromosome is commonly found, but it is not found in all cases of the disease.

functions of individual chromosomes

Relatively little is known about the specific functions assigned to the various chromosomes other than those of the sex chromosomes, which apparently determine the primary sexual characteristics of the individual. Some relationships have been established between specific chromosomes and the synthesis of components of the nucleolus in plants. Longwell and Svihla [29] have suggested that one or two chromosomal loci normally participate in the formation of nucleoli. The basis of these studies was the finding of mutant forms of wheat with twice the normal number of certain individual chromosomes and groups of chromosomes. Longwell and Svihla [29] found that mutant forms that had a doubling of chromosomes I and X had 3.0 nucleoli per cell instead of the normal 1.5 nucleoli per cell. They also noted that doubling of chromosomes XIV and XVIII increased the number of nucleoli to 2.0 per cell. When other chromosomes were doubled, there was no change in the number of nucleoli. They suggested that the specific chromosomes I, X, XIV, and XVIII were the ones primarily involved in synthesis of nucleoli and that these chromosomes differed in their capacity to produce the nucleoli. The lower numbered chromosomes were thought to be "strong" and the higher numbered "weak" nucleolus formers.

In *Drosophila,* the fruit fly, and in wheat or maize, many experiments have been carried out to define the role of the chromosomes in terms of such phenotypes as eye color and body shape or in terms of seedling, flower, and plant structure. With the aid of such studies, it has been possible for geneticists to combine studies on the frequency of mutations with studies on chromosome numbers and crossovers. From such studies, linkage maps of the chromosomes of various species have been constructed that are in a sense frequency distribution maps that predict frequency of chromosome breaks, crossing-over potential, and frequency of simultaneous transmission of one character with another. The hereditary characters tend to cluster toward the center of the chromosomes according to these maps [41]. Each of the loci of the chromosome involved in the transmission of the hereditary characteristic is referred to as a "gene," although generally a gene is simply considered to be a factor concerned with the hereditary transmission of the characteristics of the parent to the offspring, the species of origin not being a factor.

Although the functions of the chromosomes have been "mapped" in a number of species with fewer than ten chromosomes, the functions of chromosomes of man are virtually undefined at present. It is convenient to presume that genetic transmission occurs by means of the components of chromosomes, but even in this regard conclusive evidence is lacking.

The plasma-genes have been found in the cytoplasm of *Paramecia* and other species. Moreover, viruses composed of ribonucleic acid (RNA) contain sufficient genetic information to ensure their replication by infected cells. The chromosomes contain essentially all of the deoxyribonucleic acids (DNA) of the cell and relatively little RNA. It is possible that the RNA of cells may also be functional in transmission of genetic information and may be responsible for "plasmagene" effect. Accordingly, both the quantitative and qualitative role of the cytoplasm and the nucleus in hereditary transmission remain to be worked out. The present supposition, however, is that most genetic transmission takes place through chromosomal mechanisms.