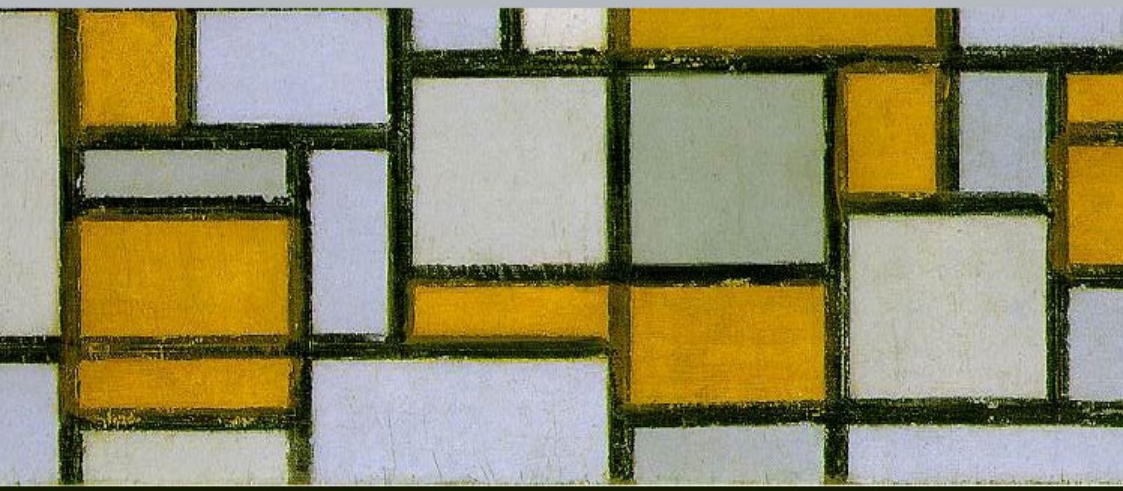
JOHN D. RAINER

The Genetics of Man in Health and Mental Illness



American Handbook of Psychiatry

THE GENETICS OF MAN IN HEALTH AND MENTAL ILLNESS

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e-Book 2015 International Psychotherapy Institute
From *American Handbook of Psychiatry: Volume 1* edited by Silvano Arietti

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THE GENETICS OF MAN IN HEALTH AND MENTAL ILLNESS

In no branch of medical science have there been more rapid, more significant, and more fascinating advances in recent years than in the understanding and application of genetics. Once the research tools and conceptual frameworks became available, psychiatry, too, finally accepted genetics as one of its foundation stones. Gene-borne and gene- external influences can now be more readily conceived as continuously interacting in human development rather than as mutually exclusive, and the study of the machinery, the processes, and the consequences of this interaction can now be seen as essential to the understanding, the control, and even the treatment of psychiatric disorder.

In the interdisciplinary setting of modern psychiatry, genetics may be thought of as an area on a map surrounded by the research fields of biochemistry, pharmacology, physiology, experimental psychology, and ethology, and the clinical pursuits of diagnosis, treatment, community and social psychiatry, and developmental and psychodynamic understanding. In the past decade and a half, major advances in cytological and molecular genetics have captured the imagination of psychiatrists and suggested a basis for the possible mechanisms of genetic influence. New approaches to the

study of the genetics of behavior have provided data on strain differences in species from drosophila to dogs, and problems of population growth and ecology have drawn attention to crucial aspects of population genetics, evolution, and the human gene pool. Meanwhile, clinicians have become more aware of individual differences in patients of all ages, in the genetic aspects of family patterns, and in hereditary differences in metabolism and response to drugs. All of these developments have opened the borders on the map described above and have made for productive communication and cooperation between genetics and the other basic and clinical sciences in psychiatry.

This, of course, was not always the case; the nature-nurture controversy, which still smoulders and breaks out occasionally, divided behavioral scientists into biologically and psychologically minded groups, and heredity and environment were thought of as separate and distinct forces. In the United States oversimplified views of one side or the other prevailed, with psychogenic or environmental forces usually given the dominant role. The behaviorism of J. B. Watson and the psychobiology of Adolf Meyer emphasized the role of external forces in molding behavior and life style; and in the transfer of psychoanalysis from Europe before and after World War II, the attention of Freud and Ernest Jones to inborn differences was largely ignored. A few psychoanalysts of that generation preserved the unitary approach; Hartmann studied inborn characteristics of the ego, and Rado

considered psychodynamics to be established on the bases of genetics and physiology. In clinical psychiatry a few American family and twin studies of the major psychoses were reported by Rosanoff, and Pollock and Malzberg in the attempt to assess the genetic contribution, but it was the publication in 1938 of Franz Kallmann's *The Genetics of Schizophrenia*, based on his Berlin family study, and in 1946 of his paper "The Genetic Theory of Schizophrenia," based on his New York State twin investigation, that for a while divided and then aroused American psychiatry to the importance of genetic factors. During his influential career Kallmann devoted his attention to many areas, including schizophrenia, manic-depressive psychosis, homosexuality, mental deficiency, aging and longevity, tuberculosis, early total deafness, cytogenetics, and genetic counseling.

Throughout the description of the various applications of genetics to psychiatry, it is well to think of the influences and interactions as taking place developmentally in time at various levels of biological organization; the atomic and molecular, the cellular and systemic, the metabolic and neurophysiological, the psychodynamic, the familial, the demographic, and the social. The psychiatric status of the organism at any given time is defined by its interaction with its surroundings, with an interplay of effective forces whose various loci are genes, chromosomes, cytoplasm; enzymes, hormones, metabolites; brain and nervous system; infectious and toxic agents and diet; parents, families, groups, and society. In the largest sense the aim of

psychiatric genetics as a scientific approach is to understand and control the etiological mechanisms both in psychiatric illness and in normal, adaptive behavior.

Interaction of Genetic and Experiential Determinants

Before any details of basic genetics or clinical application are presented, it is of prime importance to consider the problem of illustrating, conceptualizing, and describing the interaction of all types of molding forces, and in particular that between the information carried by genes and chromosomes and that provided by the natural and man-created environments. The activation or repression of genes or entire chromosomes, so obviously important in providing for cell differentiation and smooth physiological function in response to the needs of tissue and organism, is being seen more and more in terms of feedback-interaction; one model is provided by the mechanism of regulator genes outlined for bacteria by Jacob and Monod, another by hormonal control. Another example of orderly interaction at the molecular level is the production by the cells of a specific antibody in response to antigenic stimulation; less adaptive, at least to the individual, are environmentally induced gene mutations or chromosome breaks, or disruption of genetic function by viral intrusion.

At the other extreme on the scale of time and number, the mechanisms of population change and evolution are being carefully reevaluated; positive and negative selective forces in the environment, the workings of chance, and the complexity of the genetic structures of the individual and the population, all contribute to the dynamic patterns of adaptation and change.

These various basic mechanisms, by no means completely understood, but essential to the very substance of modern genetics, can make it easier to conceive of the way genetics may function in individual development and psychopathology by serving as prototypes in some kind of general systems approach. If interaction is more than co-action, the need for two forces to combine, but rather a unique process with mutual feedback, spiral development, and critical stages, proper language must be found to describe the interworking of genetic and nongenetic factors as they come to light. Meanwhile, a few examples of clinical efforts in this direction may be presented.

Psychodynamics and Genetics

The science of psychodynamics has been considered by many psychoanalysts to be part of a total biological conception of man. In Rado's scheme, for example, by the psychodynamic approach to an understanding of motivation and emotional control, it was considered possible to describe behavior problems and character disorders that would require for their complete explanation investigating the role of genetic transmission. Such an approach was certainly implicitly and explicitly formulated in the writings of Freud, who considered both the constitutional and accidental causes of neurotic disease, and who spoke of primary congenital variations in the ego and in the defense mechanisms an individual selects. Hartmann also, as part

of his interest in twins, wrote of personality structure as the result of interaction between heredity and environment. He considered character anlagen that differentiate into character traits in the course of development, and he felt that twin studies might throw light on the possible substitution of one trait for another. Genetics may thus act as a unifying principle in future psychodynamic work, providing an opportunity to recognize fundamental genetic differences among individuals and to correlate these differences with various forms of developmental interaction.

Studies of Infants and Children: Reaction Patterns

As science progresses by the interplay of theory and observation, new formulations in ego psychology go hand in hand with fresh approaches to investigation. Verifying the observations of almost any mother, child psychiatrists have turned their attention to individual differences among children, found them to be as important as maternal attitudes in shaping subsequent behavior patterns, and begun to study the details of the interaction in a longitudinal framework. As Anna Freud wrote, "inherent potentialities of the infant are accelerated in development, or slowed up, according to the mother's involvement with them, or the absence of it." The individual differences have been measured in various areas, among them sleep, feeding, and sensory responses, activity and passivity, motor behavior, and specific reaction patterns. Thomas, Chess, and Birch have identified nine

temperamental qualities in early infancy that tend to persist at least during the first two years. These are activity level, rhythmicity, approach-withdrawal, adaptability, intensity of reaction, threshold of response to stimulation, quality of mood, distractibility, and attention span and persistence. Various psychophysiological studies of neonates have also provided pertinent data.

The role of heredity in determining these constitutional variations requires further clarification, since the interaction process begins from the moment of conception and prenatal and perinatal influences come into play as well. Refined observational techniques coupled with methods of genetic analysis discussed below can be expected to clarify this intricate matter.

Interaction Models in Psychosomatic Disorders

The principle of the interlocking effects of genetic, nurtural, and social contributions in psychopathology is well illustrated in Mirsky's studies in the etiology of peptic ulcer and Spitz's formulations regarding infantile eczema. In the ulcer studies both neonates and healthy older persons were noted to vary in the degree of secretion of pepsinogen, as measured in urine and blood; this variation appears to be genetically determined. Under conditions of environmental stress, army training, for example, a large number of those who were rated as hypersecretors developed signs and symptoms of a

duodenal ulcer, but none of those in the hyposecretor group did. In Mirsky's formulation infants who are genetically hypersecretors have intense oral needs that are insatiable by the average good mother; the mother is therefore perceived as rejecting, the dependent wishes persist, and they can be revived in later life when fears of the loss of security are mobilized by environmental stress. The resultant anxiety, by pathways as yet not certain (hypothalamic, autonomic; hyperexcretion of pepsinogen, hyperchlorhydria, hypermotility, hyperadrenalism), may precipitate the ulcer in the predisposed individual.

Similar observations were made by Spitz on a group of infants institutionalized along with their unwed mothers. The infants who developed eczema differed from those who did not in a congenital predisposition and in a psychological factor originating in the mother-child relation. In particular, the infants who would develop eczema in the second six months of life showed a heightened set of responses at birth in the area of cutaneous reflexes. Psychologically their absence of eight- month anxiety meant to Spitz a retardation in affective development and led to the discovery of manifest anxiety and repressed hostility on the part of their mothers. The mothers did not like to touch their child or care for them, deprived them of cutaneous contact, and therefore refused to gratify the very need that already at birth had been shown to be increased in this group of infants. The pathways to the actual somatic lesion are again not clear, but the model for interaction provides the new kind of dynamic role for genetics in psychiatric thought.

Molecular Chemistry of Genetics

Classical Transmission Genetics

The rediscovery of Gregor Mendel's garden pea experiments at the turn of the century established the fact that single hereditary traits are determined by paired particles (later called genes) that are unchanged throughout life, independently separate during gamete formation, and are transmitted via the ovum and sperm respectively to combine again in the zygote. The sum total of the genetic constitution of an individual, as thus established in the zygote and duplicated in every somatic cell, is referred to as the genotype, and his appearance and physiological state at any given time as his phenotype. It is possible for an individual to receive the same (or an essentially indistinguishable) gene from each parent at a given locus, and under proper environmental conditions such a homozygote will exhibit the characteristics associated with the action of that gene. On the other hand, each parent may contribute a different gene (allele) at the given locus; such a heterozygote may exhibit traits intermediate to those associated with the homozygote for either gene, or he may display the same trait as a homozygote, in which case the trait is known as dominant. A trait that is not expressed in an easily discernible fashion in a heterozygote is known as recessive. A mutated gene arising with predictable frequency in the population, if not immediately lethal, will usually have a pathological effect expressed against the genetic

background of many other factors. If dominant it will be transmitted in pedigrees in the direct line of descent through the affected parent in each generation, appearing in approximately 50 percent of that parent's offspring. Recessive traits require inheritance from both parents, who, since they are usually heterozygotes, are rarely affected themselves. A child of two heterozygotes has a 25 percent risk of being a homozygote and of being affected under usual environmental conditions. While heterozygotes, or "carriers," for a given gene are relatively frequent in the population, the chance of two such individuals mating under conditions of random choice is much less common; when the gene is rare, many of such matings will be represented by consanguineous marriages. Transmission of the gene is chiefly along collateral lines, from heterozygote to heterozygote.

Since a gene produces a given trait only via a long series of steps that may be modified at every level by both prenatal and postnatal environmental forces and requirements, as well as by the action of other genes, the effects described above may vary from complete expression to total lack of penetrance. In many traits, particularly in variations within the range of normalcy in such characteristics as height or intelligence but also in graded pathological syndromes, the genetic contribution is made by the resultant effect of many genes, either all having minor intermediate effect (multifactor inheritance), or modifying the effect of single major genes.

Replication, Transcription, and Translation

For a half century this empirical body of knowledge was related to what was known of chromosome structure and processes of cell division, to inborn errors of metabolism, to the study of mutations, usually radiation-produced, and to the experimental, mathematical, and statistical investigation of populations and evolutionary processes. In the 1950s a new level of understanding was achieved through major advances in molecular genetics and cytology. For some time it had been known that the genetic material transmitting information from generation to generation was deoxyribonucleic acid (DNA). In 1953 the structure of this molecule was determined by Watson and Crick. Two sugar (deoxyribose)-phosphate-sugar chains are twisted about each other, forming a double helix. To each sugar is attached a nucleotide base—a purine (adenine or guanine) or pyrimidine (cytosine or thymine). From a sugar on one chain to the corresponding sugar on the other, there is a hydrogen bond linkage that may only take place between either adenine on one chain and thymine on the other, or guanine on one and cytosine on the other. A DNA molecule may consist of thousands of such nucleotide linkages. Replication of the DNA molecule during cell division preserves the sequence of nucleotide bases, since separation of the strands, breaking the linkages between the nucleotides, is followed by the construction by each half of a new sister chain, with the sequence complementary to the original half chain. There result two double helical

chains, each identical to the original. This model made possible an unparalleled explosion of investigation and knowledge.

The importance of the base sequence in the DNA molecule was soon realized, as the process of protein manufacture by the cell was elucidated. In very schematic form the code represented by the sequence in the double helix is transcribed to a single stranded molecule, messenger ribonucleic acid (mRNA), which is then found in the cytoplasm attached to structures known as ribosomes that move along its length. Here the code is translated, directing the sequence of amino acid assembly into a polypeptide chain. In this process specialized molecules of soluble or transfer RNA (sRNA) carry one by one in turn specific amino acids to specific codons, sequences of three nucleotide bases that code for one amino acid alone. Once formed, the chain assumes the spatial configuration of a specific protein molecule.

Mutation

Gene mutations represent a change in the genetic instruction. In the light of the above scheme, they arise from a change in the nucleotide sequence in the DNA, an error during replication possibly resulting from the action of certain chemicals or from radiation. This change will affect the transcription-translation process so that a modified polypeptide or protein will be produced. Since this product is either an enzyme or a structural

protein such as hemoglobin, the result may be disordered function or structure—for example, the loss of enzyme activity responsible for phenylketonuria, or the altered hemoglobin structure found in sickle-cell anemia.

Control of Gene Action

In the normal functioning of the above process, it is obvious that there must exist some method of control or regulation. With every cell containing the same genes, some of these must be inactive, their message never transcribed, to account for the differentiation of cell functions. In all cells there must be some feedback mechanism whereby the production of enzymes and other products is regulated at any given time according to the needs of the entire organism. There are various theories to account for such control. Jacob and Monod have studied the action in bacteria of regulator genes whose products may switch on or off the action of structural (enzyme-producing) genes depending on the presence or quantity of the substrate on which the given enzyme acts, or the end product of such action. In this operon theory genes are responsive to their surroundings; this is the most basic example of the process of interaction so central to the modern conception of genetics. In higher organisms more complex mechanisms, including the action of hormones, may play a role in the regulatory process.

Human Cytogenetics

While these advances in the molecular chemistry of genetics were being made, techniques were being developed that led to a corresponding explosion in cytogenetics, the visualization and study of human chromosomes in health and disease. As in many fields of knowledge, dramatic discoveries concerning human chromosomes followed quickly upon the perfection of new techniques. Some long-held hypotheses had to be discarded while a few careful observations came to be explained in a definitive manner.

For many decades the study of human chromosomes had been neglected. Even the number of chromosomes and the mechanism of sex determination had been matters of controversy. For a long time most textbooks perpetuated the erroneous statement that the diploid number of chromosomes in man was 48. It was known that females had two X chromosomes and males one X and one Y, but by analogy with drosophila maleness was thought to be due to the presence of only one X chromosome, insufficient to balance masculinizing genes on the autosomes. There were no satisfactory methods of correlating chromosomal or nuclear patterns with clinical abnormalities.

Sex Chromatin and "Nuclear Sex" Determination

In retrospect the first breakthrough in modern human cytogenetics

occurred in 1949, when Barr and Bertram4 accidentally discovered an important morphological difference between female and male cells. Examining neurons of the cat, they found, in some animals only, a densely staining chromatin mass applied to the inner surface of the nuclear membrane. It was soon realized that it was female cats that demonstrated this nuclear chromatin. This phenomenon was then demonstrated in other mammals and in man, where from 30 to 60 percent of the cells of a normal female show the dark-staining mass, referred to as sex chromatin or a Barr body. In 1954 a corresponding sex difference was discovered in polymorphonuclear leucocytes, where an additional small lobe is found in about one in 40 cells in females and in less than one in 500 cells in males. Because of its shape, this small lobe was called a "drumstick."

Since the sex chromatin body was found in females, who have two X chromosomes, and not in males, who have one, it was originally believed to be made up of the dark-staining regions of two such chromosomes. Later it was established that a Barr body consists of all or part of one X chromosome, one that was modified, suppressed, or partially or totally "inactivated." According to Lyon's hypothesis, this "inactivation" of one X chromosome in each cell takes place early in the development of the female embryo.

Sex chromatin determination in humans may be accomplished by examining any cellular tissue; in practice it is most convenient to study

smears made of oral mucosal cells. After swabbing the inside of the cheek gently with a gauze pad, the roughened surface is scraped with the edge of a narrow metal spatula. The buccal material is spread onto a glass slide, which is fixed in 95 percent ethyl alcohol for 30 minutes. It is then washed and stained by a nuclear stain such as thionin or cresyl violet, cleared, and mounted; between 100 and 200 cells are then examined.

It was not long before the process of "nuclear sexing," as it was then called, was applied to certain cases of human infertility and abnormal sexual development. In 1954 female patients with gonadal aplasia (Turner's syndrome) were reported to be chromatin-negative, that is, to lack the nuclear chromatin body. Such females tend to be of short stature and sexually infantile, and their ovaries are reduced to streaks of connective tissue. Associated defects such as webbed neck and increased carrying angle of the arms are often present. Occurring with an estimated frequency of 0.2 to 0.3 per 1,000 females, Turner's syndrome may include slight intellectual impairment but not severe mental deficiency. Because of the absence of nuclear chromatin, early investigators considered such patients as "chromosomal males" with some form of sex reversal. Although this interpretation was not generally accepted, it was finally corrected only by later findings, which are described below.

A second classical example of nuclear sex anomaly was Klinefelter's

syndrome, characterizing males with small atrophic testes, sterility, gynecomastia, and increased excretion of gonadotropin. Occurring in about one in 500 male births, it accounts for about 1 percent of male mentally retarded patients in institutions. In 1956 a high proportion of patients with this clinical syndrome were found to be chromatin-positive; they were for a time incorrectly termed "chromosomal females," presumably with two X chromosomes. Further elucidation of the etiology of this disorder also awaited study of the chromosomes themselves and direct observation of the patients' sex chromosome constitution.

Technical Advances In Human Cytogenetics

The next set of studies in human cytogenetics followed the perfection of methods for observing human chromosomes microscopically. Earlier investigations were done mostly on testicular biopsies, but degenerative changes as well as clumping and overlapping of chromosomes led to inaccurate counts. The introduction of tissue culture methods made available a better source of cells in the process of mitotic division, the stage in which the chromosomes are distinguishable. Treatment with colchicine arrested dividing cells in this stage, and the use of hypotonic solutions swelled the nuclei, spreading the chromosomes and separating them for examination before final staining of the cells in slide preparations. Photography under the oil immersion lens revealed the chromosomes as X-shaped bodies, each

representing a single chromosome in the process of dividing. First applied to skin biopsy material and bone marrow, these techniques have been variously modified and at present are applied most practically to lymphocytes of peripheral blood.

Suspended in their plasma and stimulated to divide by the addition of phytohemagglutinin, such cells are protected against bacterial contamination by antibiotics. After three days of incubation at 37°C, they are ready for harvesting after being arrested at the cell division stage by adding colchicine or a derivative of it. The addition of hypotonic sodium citrate solution is followed by fixation, slide preparation, staining, clearing, and mounting.

Normal Human Karyotype

In 1956 these new techniques resulted in the demonstration of 46 chromosomes as the correct number in man. It became possible to study clear and easily examined preparations of human chromosomes, to photograph them, and to enlarge, cut out, pair, and mount them in order of decreasing length. Such an arrangement is called a karyotype; a diagrammatic representation thereof is called an idiogram.

Chromosomes may be distinguished from one another by their length and by the position of the constriction called the centromere, the point at which the two parts of the dividing chromosome still remain joined. The

centromere may be median (metacentric), submedian (submetacentric), or subterminal (acrocentric) in location; in many chromosomes of the latter type satellite bodies may be seen projecting from their short arm.

When arranged in order of decreasing size, the human chromosomes fall into seven groups, which were standardized at a historic meeting in Denver in 1960. The groups may be clearly distinguished, and chromosomes within a group can often be recognized with a high degree of probability. In line with the system proposed at the Denver meeting, the description of the chromosomes is as follows:

Group 1-3. (A) Large chromosomes with approximately median centromeres. The three chromosomes are readily distinguished from each other by size and centromere position.

Group 4—5. (B) Large chromosomes with submedian centromeres. The two chromosomes are difficult to distinguish, but chromosome 4 is slightly longer.

Group 6-12. (C) Medium-sized chromosomes with submedian centromeres. The X chromosome resembles the longer chromosomes in this group, especially chromosome 6, from which it is difficult to distinguish. This large group presents the major difficulty in identification of individual chromosomes.

Group 13-15.(D) Medium-sized chromosomes with nearly terminal

centromeres (acrocentric chromosomes). Chromosome 13 has a prominent satellite on the short arm. Chromosome 14 has a small satellite on the short arm. No satellite has been detected on chromosome 15.[1]

Group 16-18. (E) Rather short chromosomes with approximately median (in chromosome 16) or submedian centromeres.

Group 19-20. (F) Short chromosomes with approximately median centromeres.

Group 21-22. (G) Very short, acrocentric chromosomes. Chromosome 21 has a satellite on its short arm. The Y-chromosome is similar to these chromosomes.

Further conferences were held in London in 1963, in Chicago in 1966, and in Paris in 1971, with the aim of increasing the accuracy of chromosome identification. The presence of secondary constrictions and the determination by radiographic means (incorporation of radioactive thymidine into replicating chromosomes) of the time sequence of chromosome replication were among the methods suggested at the London conference; in Chicago a standard nomenclature was adopted for describing the human chromosome complement. More recently new staining techniques were reported that promise to make each chromosome individually recognizable by disclosing banded regions; among the distinguishing characteristics are fluorescent patterns seen after exposure to quinacrine derivatives and deeply colored

bands using various modifications of Giemsa staining methods.

Chromosomal Abnormalities

Within three years after the correct determination of the human karyotype, and even before the numbering system was standardized, important discoveries were made correlating abnormalities in the karyotype and clinical syndromes. The first group of these abnormalities arose from the presence of an abnormal number of chromosomes and resulted from a process known as nondisjunction in the formation of the gamete (sperm or ovum). Instead of the two members of a given pair of chromosomes separating, each one going into a separate sperm cell (in the male), or into the ovum and polar body, respectively (in the female), they both go into the same gamete, producing two kinds of abnormal gametes, those with two chromosomes of a given pair and hence with one chromosome too many, or with none of that pair and hence one too few. When united with a normal sperm or ovum, such a gamete yields a fertilized ovum (zygote) with either 47 or 45 chromosomes in all. Similar processes of nondisjunction at an early cleavage stage of the zygote, resulting in cells with even more than 47 chromosomes, have been found in conjunction with the X and Y chromosomes. It is also possible in such cases that cells of more than one kind are formed, each one of which perpetuates its line, giving rise to individuals with cells of two or more types. This phenomenon is known as mosaicism.

The first condition found to be associated with a chromosomal anomaly was mongolism, preferentially referred to as Down's syndrome. The association of this syndrome in the preponderance of cases with children born to older mothers, and the one-egg twin concordance rate of close to 100 per cent, foreshadowed an early germinal, possibly a chromosomal, defect as the responsible agent. Early in 1959 tissue culture methods showed that patients with Down's syndrome had 47 instead of 46 chromosomes and that the additional chromosome was one of the smallest chromosomes, no. 21 in the conventional numbering system. Arising by nondisjunction (especially in the female, as is suggested by the association of the condition with advancing maternal age), the extra chromosome, small as it is, causes widespread morphological and biochemical abnormalities.

Some cases of Down's syndrome, especially those born to younger mothers or those with a familial concentration, were assumed for a while to have a normal chromosome complement. However, upon closer examination of the karyotype, one of the chromosomes of the 13 to 15 group was found to have attached to it the long arm of an extra chromosome 21. Thus there was a translocation of chromosomal material, a situation that may be transmitted from generation to generation. If two normal chromosomes 21 are present, in addition to the 15/21 translocation chromosome, the individual is affected; if only one is present, the individual is normal. In the latter case, however, he or she may be a "carrier," that is, may bear affected children, by producing a

gamete with both the translocation chromosome and a normal chromosome 21. Translocations have been found also between chromosomes 21 and 22. From a practical point of view the translocation mechanism for producing this syndrome is very important. For most mothers of a child with Down's syndrome, the chance of having a second such child is very small, hardly greater than for any other woman of the same age (1 in 600 altogether, up to 1 in 50 in mothers over 45). A mother with a 15/21 translocation has a much higher risk (about 10 percent) of having a second affected child, apart from that of having children who are carriers. If the father has the translocation, the empirical risk of having an affected child is lower (2 to 3 per cent). Microscopic chromosome examination is therefore strongly indicated in counseling such families.

Other conditions with trisomies of autosomes have been described that are rare in live-born infants and usually result in early death. One of the conditions, involving a chromosome of the D group, is characterized by symptoms that include microphthalmus, harelip, cleft palate, and polydactyly, frequently accompanied by congenital heart defects, in another, in which an E group chromosome is involved, is characterized by micrognathia, low-set ears, overlapping of fingers, and other skeletal and cardiac defects.

Abnormalities Involving Sex Chromosomes

After interest had been aroused in sexual abnormalities with anomalous chromatin patterns, it was not long before the techniques of studying human karyotypes were applied to these conditions. Chromatin-negative Turner's syndrome was found to be associated with only 45 chromosomes, one of the sex chromosomes being missing. The resulting sex chromosome constitution was first called the XO condition, "O" indicating simply the absence of a chromosome normally present; in the Chicago nomenclature it is called 45, X. Apparently this condition may originate by nondisjunction in the formation of either the sperm or the egg. Thus, while normal sperm cells have either an X or Y chromosome (in addition to 22 autosomes), the nondisjunction phenomenon may yield sperm cells having both X and Y (XY) with 24 chromosomes in all, or neither (O) with 22 chromosomes in all. Similarly, while normal ova all have one X chromosome, the abnormal ones may have two (XX) or none (O). Fertilization of an O gamete by a normal X gamete results in the karyotype of Turner's syndrome.

In similar fashion patients with Klinefelter's syndrome are known to have 47 chromosomes with an extra X chromosome (XXY), brought about by the union of an abnormal XY sperm with a normal ovum, or an abnormal X ovum with a normal Y-bearing sperm. A third classic example of chromosomal abnormality in the human is represented by females, sexually infantile and amenorrheic, with an XXX chromosome pattern.

The sex chromatin pattern in these anomalies can now be shown to be related in a simple way to the chromosome structure. The number of nuclear chromatin patches is always one less than the number of X chromosomes found—hence Turner's syndrome has none, Klinefelter's has one, and the triple X female has two. In terms of the Lyon hypothesis, this finding can be explained by the inactivation of all X chromosomes in excess of one. At the same time it has been established that the presence of a Y chromosome is necessary and sufficient for maleness, since the XO individual is female with only one X chromosome but no Y, while the XXY, possessing two X chromosomes but also possessing a Y, is male.

These sex chromosomal anomalies are the prototypes of more complex pictures that have been reported. Nondisjunction during later cell divisions after the zygote is formed may produce such abnormalities as XXXY or XXXXY individuals (males similar to Klinefelter's syndrome but with severe mental deficiency) and many varieties of mosaicism. It has been estimated that one in every 150 newborn infants has a chromosome aberration identifiable by present techniques.

Chromosomal Abnormalities and Psychiatric Syndromes

Aside from the importance of human chromosome analysis for diagnosis and counseling, its value in unraveling the processes of gene action

is only beginning to be exploited. For one example, the correlation of specific disorders with syndromes associated with chromosome abnormalities may serve to localize the genes involved on particular chromosomes or the metabolic (enzymatic) pathways of gene action and may also help to distinguish nosological subgroups in major diagnostic categories.

In the major syndromes of psychiatric importance chromosomal findings have been equivocal. Only a small proportion of schizophrenic patients seem to display a sex chromosome abnormality; conversely a few of the mentally defective patients with abnormal karyotype show psychotic or schizophreniclike behavior.

Klinefelter's syndrome, with 47,XXY karyotype and its variants, leads to degrees of eunuchoid habitus and weak libido, low marriage rate, often mental deficiency, and personality disorders ranging from inadequate personality and delinquency to symptoms of schizophrenia. This trisomic condition has been found three times as frequently in mental hospitals as among newborns. If this figure is upheld it will still have to be clarified whether the patients have psychotic-like syndromes resulting from the chromosome imbalance or whether the chromosomal syndrome precipitates an otherwise determined psychosis by adding an additional biological or social burden. Similar considerations apply to the extra X chromosome in the female, the 47,XXX syndrome. Once misnamed "superfemales," those who

have been found in clinics and hospitals are often mildly retarded and socially withdrawn; they seem to be found more often than expected in mental hospitals, but their incidence at birth (1 in 1,000) is only a rough estimate. Schizophrenia in women with the XXX karyotype has recently been studied by Vartanyan and Gindilis.

Turner's syndrome, typically a short and sexually undeveloped female, is associated with the absence of the second sex chromosome, leaving 45 chromosomes with a single X. If emotional reaction, sexual immaturity, and body defects play any role in the extra X syndromes described above, they do not seem to result in any disturbance here, for these girls and women have been described as resilient to adversity, stable in personality, and maternal in temperament. They are not mentally retarded except in some nonverbal skills centering about space-form appreciation and constructional skills. This finding is significant as one of the few examples of a specific intellectual correlate of a karyotypic defect.

A great deal of interest has been generated in the 47,XYY anomaly. Although noted in the general population, males with this chromosome constitution were found in seeming excess in correctional institutions where they were noted to be tall, mentally deficient, and prone to aggressive behavior patterns. The specificity of this syndrome has been questioned, especially since the frequency of XYY males in the total population is not yet

accurately known.'" Fluorescent staining techniques in buccal epithelial cells should be able to provide better data both on the incidence of the karyotypic abnormality and its possible consequences in the course of development. Cases studied so far, including a pair of adolescent twins, suggest that at least some of these men are usually passive, withdrawn, inadequate, and docile, but under stress they may exhibit impulsive behavior. There is also suggestive evidence that these periodic episodes have a seizurelike course and that the electroencephalogram may be abnormal.

Further information on the relationship between chromosome imbalance and mental symptoms may one day elucidate some of the genetic mechanisms in behavior disorders. An analogy has been provided in studies of the fruit fly by the correlation of behavioral response with contributions from specific chromosomes.

Methods of Investigation in Psychiatric Genetics

Pedigree Method

The study of individual families or pedigrees has often been used to suggest forms of genetic transmission for larger-scale investigation or to provide tentative material on rare, well-defined pathological conditions. They have to be supplemented by the study of more representative samples with proper attention to statistical methods of correcting for ascertainment.

Census Method

In geographically confined populations, small enough to be visited individually, and with good medical and demographic records, it has been possible to study the population and family distribution of diagnosable psychiatric disorders; this method has provided some excellent reports in certain Scandinavian areas.

Family Risk Studies

An extension of the pedigree method, studies of family risk (sometimes referred to as contingency methods) have as their goal comparing the expectancy risk for a given condition in the relatives of affected individuals with that in the general population. A number of pitfalls must be avoided. The

affected individuals must be diagnosed according to uniform criteria, and they must represent a consecutive series of patients (or a random sample thereof). They are designated then as index cases, or probands. All relatives in the desired categories must then be located and diagnosis made. Since one is interested not in the incidence (new cases) or even the prevalence (total cases) but rather in the expectancy rate (cases that may arise during the lifetime of the relatives), it is necessary either to wait for many years or more practically to apply a correction method. A simplified method often used is the Weinberg abridged method. A manifestation age interval is derived clinically; in schizophrenia, for example, it is usually taken at 15 to 45 years. The number of cases found among a given category of relatives (the numerator) is related to a denominator that is not the total number of relatives in this category, but rather that number diminished by all of those who have not reached the earliest manifestation age and half of those still within the manifestation period. This method yields a risk figure, representing the expectancy of developing the given condition for those who will live through the manifestation period. This figure can then be compared with risk figures for other groups of relatives and for the general population. The latter have been determined in many cases by total or sample population studies, or by studies of the relatives of control patients.

Twin Family Method

An extension of the family risk method to families containing twins makes possible a series of further approaches to understanding the complementary roles of nature and nurture, heredity and environment.97'98 First used by Galton, the method depends upon the occurrence of two types of twins, those derived from a single fertilized ovum that has split and developed as two separate individuals ("identical," monozygotic, or one-egg twins) and those derived from two ova, fertilized by two different spermatozoa during the same pregnancy ("fraternal," dizygotic, or two-egg twins). In the first case the twins are always of the same sex (barring a rare sex chromosome loss early in embryonic division, which may result in a pair of one-egg twins made up of a normal male and a female with Turner's syndrome). On the average dizygotic twins are one-quarter of the time both male, one quarter of the time both female, and half the time of opposite sex. Zygosity determination can be made with a high degree of accuracy by similarity of somatic characteristics. The accuracy is further increased by comparison of fingerprints and blood groups, while immunological methods such as reciprocal skin grafting may provide certainty in individual pairs where intensive study requires and warrants such procedures. Monozygotic twins are born with the same genotype; dizygotic twins are as similar genetically as any pair of sibs.

In the twin family method the index cases are twins. Expectancy rates can be compared between monozygotic twin partners, dizygotic twin

partners of the same sex, dizygotic twin partners of opposite sexes, full sibs, half sibs, and step sibs. This method provides a graded series of genetic relationships and a differently graded series of environmental ones; the extent to which the risk in the various categories of relatives corresponds to the genetic similarity bears a relation to, or is a measure of, the genetic contribution to the etiology of the condition. For example, if the expectancy in monozygotic twins is higher than that in dizygotic twins of the same sex (despite the environmental similarities) and that in dizygotic twins is close to that in full sibs (to which they are genetically equivalent), there is a measurable genetic contribution. Another way of separating genetic and environmental influences would be to study identical twins reared apart from birth, preferably in homes with disparate social and psychological settings, but such pairs who also present a particular syndrome are rare.

There are a number of cautions and misunderstandings about twin studies to be noted. Before using the twin concordance method, it is necessary', for example, to determine that a condition to be investigated is no more prevalent in twins than in single-born individuals. In doing a study the sample of twins should be complete, with the expected proportion of monozygotic and dizygotic pairs, and the diagnosis of zygosity and that of illness should be made by separate persons without knowledge of the other's findings. In interpreting the results of twin studies, the assumption of comparable environmental patterns for monozygotic twins and dizygotic

twins, at least those of the same sex, has been questioned; yet observation of twins and their families has often shown similar family dynamics and role assignment—twin dependency, parental need to distinguish, and so forth—with both types of twins. Indeed, monozygotic twins are often more disparate in size and vigor at birth than dizygotic ones. Finally it should be realized that it is not necessary to have 100 percent concordance in monozygotic twins to postulate a genetic contribution; provided they are sufficiently higher than the dizygotic rates, monozygotic concordance rates of under 50 per cent, for example, can be shown by analysis of variance techniques to indicate a high heritability value.

Co-Twin Control Studies

The use of longitudinal data from selected pairs of monozygotic twins, particularly those discordant or dissimilar with respect to the overt expression of a behavioral trait or syndrome, may serve to point out important developmental factors. Among the reported case histories of twins and other sets of persons of multiple birth, the study of Rosenthal's group on the aptly named Genain quadruplets is particularly notable because of its thoroughness and its adherence to the concept of heredity-environment interaction. Although all members of the set were found to be schizophrenic, their psychoses varied in symptomatology as well as in intensity.

Other investigations of this type include the series of homosexually dissimilar twins studied by Rainer, Mesnikoff, Kolb, and Carr. Obtaining data through psychiatric anamnesis, family interviews, and free association, these studies paid particular attention to: (1) the prenatal fantasies and wishes of each parent about the sex of the expected child; (2) the attitude of the parents toward the twins' birth; (3) the family significance of the naming, both as established before birth and as modified by the birth of the twins; (4) the parental efforts at differentiating the twins; (5) the occurrence of physically distinguishing features in the twins; (6) the emotional connotations of such features to the parents and the extended family; (7) the effect of such bodily distinctions on the differential mode of mothering for each twin; (8) the differing object relations of the twins from birth onward; (9) the attitude of each twin to his body and to his self, as perceived and as seen ideally; (10) the fantasy life of the twins, particularly in the sexual area; and (11) the superego growth of the twins, particularly in relation to sexually allowed and prohibited forms of activity. Benjamin studied a pair of male twins concordant for asthma but dissimilar with respect to a number of important psychological features, in the context of seeking to "conceptualize most complex behaviors in terms of different sorts of interactions between innate and experiential constants and variables."

In a pair of twins concordant for the XYY chromosome anomaly, but dissimilar in the degree of control over episodic impulsive behavior, Rainer,

Abdullah, and Jarvik noted the mother's search for personality differences at birth, and the occurrence of petit mal seizures in one twin at the age of three. It was suggested that these early events may have set a double pattern—focusing of the mother's concern on one twin as being psychiatrically and neurologically abnormal, and a protective and caring response on the other child's part, which helped him to strengthen his control and responsibility over himself. As in all of these studies, similarities in underlying personalities were noted, particularly in projective testing, with differences in overt behavior then attributable suggestively to patterns of family dynamics as well as to physiological differences.

In the study of identical twin pairs discordant for schizophrenia by Pollin and his co-workers, again there were physiological differences, namely, lower birth weight for the subsequently schizophrenic twin, that directly or in interaction with family dynamic patterns may have influenced their development.

These studies help one to understand that genes actually determine a norm of reaction, the exact expression of which depends on many prenatal, perinatal, and postnatal interactions. The pathways are labyrinthine that lead in twins from the identical molecular structures that constitute the genic patterns to the manifestations in later life of behavior traits; minor shifts in the dynamic process at nodal points may lead to wide phenotypic divergence.

Preconceived ideas on the locus of such nodal points should be regarded with caution. A spiral-like development toward marked behavioral dissimilarity may arise not only from postnatal influences on the twins but also in the prenatal stages of development. Infant, childhood, adolescent, and adult experiences may thereafter precipitate a single gene effect or shape the expression of a polygenic trait in a unique way.

Adoption Studies

The physical separation from their biological parents of children reared in adoptive homes offers a valuable method of weighting genetic and environmental influences. Some studies involving adopted children have compared those with affected biological parents to those with unaffected biological parents, while others have compared biological and adoptive parents and other relatives of affected adopted children. Some of the findings in these kinds of studies are discussed in Volume Three, Chapter 25, of this handbook in connection with genetic studies in schizophrenia (Rosenthal).

Longitudinal Studies

Longitudinal studies of high-risk infants and children are of the greatest potential value in learning about the role and vicissitudes of genetic predisposition in mental illness. Since there is evidence for increased risk

with greater genetic loading in a given syndrome, children of one or of two affected parents may be followed, comparing them with their sibs and with control children, searching for early behavioral, biochemical, neurological, psychophysiological, and clinical signs, for patterns of development, and for protective factors.

Other Methods of Genetic Investigation

Of course, the most direct way of establishing genetic etiology would be to identify errors in the genetic code itself; the closest available approach is through identification of a specific enzyme deficiency or modification, particularly in the brain or nervous system. This may be done by electrophoretic methods or by studying products of intermediate metabolism. Loading techniques—tolerance tests—may make such deficiencies more obvious in the case of heterozygotes. Correlation of psychiatric symptoms with chromosome anomalies has been discussed; more subtle chromosomal changes will be detected with the perfection of new staining techniques, as well as with techniques of cell hybridization.

A method for establishing homogeneous genetic categories is the study of genetic linkage; a syndrome may be associated with the effect of a single gene if it appears to stem from a locus on the same chromosome with, and at a given distance from, the locus of another known gene. In principle linkage is

suggested by the detection of pedigrees in which there is a reduced frequency of recombination between genes at two particular loci; for example, depression and color blindness, occurring in the same family, may be found usually together or usually separately.

The correlation of psychiatric syndromes with certain physical characteristics—blood types, dermatoglyphics, constitutional habitus—may be a lead to the presence of a genetic basis. Finally, in cross-cultural studies, if variations in the frequency of a syndrome across different populations are determined only by population-genetic variables, such as consanguinity, genetic drift, or selection factors, the syndrome is more likely to have a genetic basis; if, however, there are strong differences in prevalence that are determined by cultural and environmental factors and that are not due to differences in diagnostic procedures, the genetic contribution, although it may still be present, will be more difficult to detect.

Genetics and Psychopathology

Schizophrenia

For over 40 years family and twin studies, studies of adopted children, and longitudinal studies, both retrospective and prospective, have yielded data consistent with the presumption of a necessary, although not sufficient, hereditary basis for schizophrenia. From the point of view of the present discussion, four themes may be noted in appraising this area of research today. The first is the need to define more precisely the significant genetic and environmental influences; the second is to find better ways to describe their interaction; the third is the increasing evidence that genetic determination seems to vary with the severity of the illness and to bear a relation to newly delineated clinical types; and the fourth is the emergence of longitudinal studies that promise to throw light on developmental mechanisms and the natural history of the condition.

Because of modern treatment and community care methods, the marital rates of schizophrenic patients have increased, resulting in a higher number of fertile marriages and higher overall reproductive rates; therefore, the need for better understanding of genetic data for use in counseling and child-care programs is evident.

Affective Disorder

Studies of families and twins have played an important role in both the nosology and etiology of affective disorder. Earlier reports have focused on manic-depressive illness. In his classic investigation of this syndrome, Kraepelin observed large numbers of relatives who had the same illness, but he did not find an increase in dementia praecox among these relatives. In most European and American populations the general rate for manic-depressive psychosis varies between 0.4 percent and 1.6 per cent, though in a few special situations, such as isolated populations, rates of as low as 0.07 percent and as high as 5 or 7 percent have been found. An excess of females has been consistently observed. In the case of parents, sibs, and children of manic-depressive index cases, the expectancy rates are much higher, with a morbidity risk in first-degree relatives of about 20 percent reported in earlier studies. With both parents affected, the morbidity risk in children has been found to be as high as 40 per cent.

In the largest twin family study that has been reported, Kallmann located 27 one-egg and 58 two-egg pairs. In this series the expectancy of manic-depressive psychosis varied from 16.7 percent for half sibs to 22.7 and 25.5 percent for sibs and two egg co-twins, respectively, and 100 percent for one egg cotwins. Parents of index cases showed a rate of 23.4 percent. Since only patients admitted to a mental hospital, and hence the most severe cases, were included as index cases, the apparently perfect concordance rate of 100 percent for one-egg twins was considered an artificial maximum value. Other

twin studies corroborated these data.

Recent investigations have tended to subdivide affective disorders into two subgroups, bipolar illness with periods of mania, and unipolar illness with symptoms limited to recurrent depression. Family studies conducted in these two groups have shown different morbidity risk in relatives, with the bipolar cases showing more genetic loading than the unipolar cases or than the earlier combined groups. A 34 percent risk was found, for example, in the first-degree relatives of bipolar patients studied by Winokur. Moreover, both bipolar and unipolar illness have been found in the first-degree relatives of bipolar cases, while families of unipolar probands have shown only unipolar illness.

These data seem to indicate that bipolar and unipolar illness are different with regard to their genetic component, although the nature of the genotype of the unipolar relatives found in bipolar families remains in question. Much current research is directed toward exploring further genetic heterogeneity in the bipolar group of affective disorders. Asano attempted to delineate subgroups of manic- depressive illness on the basis of clinical symptoms, with a “typical” group showing manic-depressive symptoms in a relatively pure form, and an “atypical” group showing clouding of consciousness, or schizophrenic or severe autonomic symptoms. The typical forms were found to have a greater and more specific genetic loading than the

atypical forms. Some studies have divided the group according to time of onset, with earlier onset associated with more severe genetic loading, later onset with a negative family history; while others have classified patients on the basis of their response to pharmacological treatment. In the latter category is the proposal by Pare and Mack to differentiate genetically between patients and affected family members who respond only to MAO inhibitors and those who respond only to tricyclic antidepressants. Similar studies are in progress with relation to lithium response.

Kallmann and Stenstedt favored an autosomal dominant form of inheritance in manic-depressive illness, with incomplete penetrance and variable expressivity. Rosanoff in 1934 and currently Winokur and Tanna support the presence of at least two dominant factors in the transmission of bipolar affective disorder, one X-linked, the other autosomal. Perris has supported X-linked transmission only in unipolar cases. Other investigators have reported data on ancestral secondary cases that are consistent with a polygenic hypothesis. None of these results are really contradictory, as one of the genes involved in polygenic inheritance may well be X-linked.

The X-linked hypothesis is based on the observation of an excess of females in the sex ratio of manic-depressive illness and the rarity of father-to-son transmission. Recently Reich, *et al.* reported on linkage studies between manic-depressive illness and two X-linked genetic markers—Xga blood group

and color blindness.

From a psychodynamic point of view Rado described the psychological characteristics of the individual predisposed to manic-depressive psychosis as a tendency to emotional overreaction from infancy, a persistent alimentary dependent state, a strong craving for gratification from without, and an intolerance to pain. He considered the depressive spell to be the final stage of an etiological progression beginning with the genotype. Further data regarding modification of symptoms by developmental factors were provided by the New York study of persons totally deaf since birth or early childhood. Although the prevalence of affective illness did not differ from that among the normal hearing population, there was a decrease in symptoms of guilt and retarded depression, with paranoid symptoms or agitation taking their place. It was hypothesized that the tenuous nature of early object relationships played a role in this modification.

Involutional depression was considered by Kraepelin to belong to the large group of manic-depressive psychosis. Kallmann found an elevated risk of schizophrenia in the relatives of probands with involutional melancholia, with no increased risk for manic-depresssive psychosis. He considered the syndrome to be pathogenetically complex and genetically associated more closely with the group of schizoid personality traits than with manic-depressive psychosis. Other investigators found an increased morbidity risk

for affective illness in the relatives of involutional probands. These discrepancies are probably due to differences in diagnostic criteria.

Criminality

Early studies of twins involving criminal behavior suffered from sample selectivity and heterogeneity; they tended to show high concordance rates for both monozygotic and same-sex dizygotic twins. This distribution of concordance rates led genetic investigators to suspect a large environmental role in the pathogenesis of criminal behavior. Individual pairs of twins have been described with divergent overt histories, and it would seem to be more appropriate to study specific personality traits leading to a life of crime rather than criminal behavior itself. The current status of the role of chromosomal abnormalities in criminal behavior has been considered earlier in this chapter.

Intelligence and Mental Defect

There is perhaps more controversy today about the role of heredity in intelligence than any other aspect of behavior genetics; the value of early childhood education, the nature of learning, the problem of underprivileged groups, and innumerable school policies have become involved with this issue. The question often narrows down to one of priorities in making very

practical decisions. Underlying much of the divergence of conclusion is the basic difficulty of measuring intelligence apart from environmental influence. Intelligence scores, largely consisting of IQs, show remarkable correlation with genetic closeness; these similarities persist in longitudinal studies of twins, for example, and in twins reared apart since early life. It is not so clear yet what factors are measured by the various tests, or how their results are affected by such environmental factors as maternal health and nutrition, or communication and educational patterns at home and in school.

A valuable contribution to the role of communication in intelligence was made by the study of a group of 33 pairs of twins discordant for early total deafness. In these pairs the verbal IQs showed significant difference that disappeared in the performance scales. The role of emotional factors in learning, both those associated with interpersonal channels of acceptance and identification and those related to security and motivation, preclude simple formulations.

In the field of mental defect some of the data are more clear-cut. Mental deficiency syndromes based on specific gene mutations and chromosomal aberrations are well known, although there are intelligence differences among persons with such syndromes that must be explained on other genetic or environmental grounds. According to Reed and Reed,s8 however, these specific genetic factors, together with obvious infectious or birth-traumatic

incidents, account for barely half of persons with IQs below 70. These authors consider that polygenic inheritance is responsible for most of the rest, with social deprivation usually playing a secondary or modifying role. In any event they conclude that five-sixths of persons in the given lower IQ range have had at least one parent or an aunt or an uncle similarly retarded.

Aging and Life Span

In human populations there have been a number of studies relating the life span of offspring to that of their parents. In Pearl's work longevity ("regarded as a single numerical expression of the graded effects of all the forces that operate upon the individual, innate and environmental") was investigated by comparing the ancestors of two groups of persons, one a group of persons still living at 90 years and above and the other a random group of individuals. The sum of the ages at death of the six immediate ancestors of the index cases was significantly greater in the longevous group than in the comparison group.

The most extensive and carefully followed investigation of aging has been that conducted in the Department of Medical Genetics of the New York State Psychiatric Institute since 1945 by Kallmann and various colleagues and continued at the present time by Jarvik and associates. These investigations started with 1,603 twin index cases over the age of 60 and followed the

mortality patterns of 584 pairs where both twins qualified as index cases. The length of time between the death of the first twin and the death of the second twin has been consistently greater in the dizygotic pairs than in the monozygotic pairs. These studies also confirmed the relationship between the mean life span of the twins and their sibs and the age of death of their parents. The investigators felt that life span potential was demonstrated to have a genetic basis that could be assumed to follow the multifactor type of inheritance. Also studied were intrapair differences in psychometric test scores, which were larger for dizygotic than for monozygotic twins. There was some indication that stability of intellectual performance was associated with survival.

In searching for possible biological concomitants of aging, Jarvik and her colleagues undertook chromosome examinations of peripheral blood lymphocytes to determine whether there were increasing deviations from the normal chromosome number with increasing life span. Such losses in peripheral blood lymphocytes might reflect similar aneuploidy in glial cells. As compared with a group of young individuals, an excess of chromosome loss was found in the aged women but not in the aged men. The chromosome loss among aged women was random and not limited specifically to C group chromosomes; in the aged males, although they showed no greater frequency of overall chromosome loss than young males, the chromosomes that were lost were largely in the G group.

Finally a higher frequency of chromosome loss was found by Nielsen, *et al*., and by Jarvik and her associates in the peripheral leukocytes of women with organic brain syndrome compared with other women of comparable age. In the New York study a significant increase in the frequency of chromosome loss was found in the women who had organic brain syndrome without evidence of cerebral arteriosclerosis, compared with women without organic brain syndrome. The relationship between chromosome loss and organic brain syndrome in males, however, appeared to be purely random. In women a positive association between chromosome loss and memory loss was also demonstrated by psychological testing.

Genetics of Psychosexual Development

Intersexual Conditions

Concerning the genetic aspects of intersexual conditions, recent findings related to chromosomal abnormalities have already been discussed. Not all sexual anomalies, however, are by any means associated with karyotypic changes. Most hermaphrodites with both testicular and ovarian tissues are found to have normal karyotypes, although some are mosaics. A few pseudohermaphroditic states, although distinguished by normal karyotypes, are apparently caused by gene-borne influences. Among them are the testicular feminization syndrome (male karyotype with testicular tissue, but female habitus and genitalia) and some instances of the adrenogenital syndrome (virilization in the female).

What one can say is that the chromosomal pattern determines the differentiation of the gonad, while the subsequent course of development—duct systems and genitalia—is hormonally controlled. More precisely the phenotypic sex (type of gonad) is the result of sex-determining genes on all the chromosomes. Male-determining genes are present strongly on the Y chromosome and probably on other chromosomes as well. Female-determining genes are probably on the X chromosome and may also exist on the autosomes. Normally the strong male determiners on the Y chromosome shift the balance in the direction of maleness. Without this chromosome

female determiners tend to exert such a strong influence that the individual develops as a female.

Regarding the management of patients with doubtful sex, it is generally thought to be desirable to determine the most suitable sex as early as possible in life, considering the chromosome pattern as well as the anatomy, and, after surgical and hormonal treatment, if necessary, to rear the child in the chosen sex.

Male Homosexuality

In the case of homosexuality earlier hypotheses implied that some male homosexuals might have a female chromosome structure. They were based on the finding of a greater proportion of males among their sibs than would be expected normally. These inferences were criticized on statistical grounds and could not be confirmed in chromatin studies on various series of male homosexuals, which showed negative sex chromatin patterns. Nevertheless, in a group of 401 consecutive admissions of males diagnosed as homosexual at the Bethlem Royal and Maudsley hospitals, these patients showed a later birth order and a high maternal age, with a variance in the latter as great as that in Down's syndrome. These data were interpreted by Slater, as supporting a hypothesis of heterogeneity in the etiology of male homosexuality, with some of them possibly connected with a chromosomal

anomaly, others associated with social and psychological causes. Moreover, a number of case reports linked homosexuality, transvestitism, and pedophilia in patients with Klinefelter's syndrome. Recent reports of abnormal patterns of hormone excretion in homosexuals, if confirmed, raise questions regarding the role of endocrine imbalance as cause or effect.

Kallmann's investigation of a series of male twins with homosexuality was interpreted as suggesting a gene-controlled disarrangement between male and female psychosexual maturation patterns. Almost perfect concordance was found in a series of 40 monozygotic twin pairs, whereas in 45 dizygotic pairs the degree of concordance was no higher than that expected on the basis of Kinsey's statistics for the general population. In the explanation of these concordance data, sexual behavior was considered to be part of the personality structure rather than the gonadal or hormonal apparatus. Not ruling out the possibility that some male homosexuals, particularly the infertile ones, might have been intersexes, Kallmann generally put aside this special explanation, along with other theories of single-factor causation, in favor of a range of genetic mechanisms capable of disturbing the adaptational equilibrium between organic sex potentialities and psychosexual behavior.

It is of historical interest to quote in this connection the opinion expressed in 1931 by Goldschmidt, a pioneer in the study of intersexuality in

insects:

> As far as human homosexuality is concerned, the biologist must be extremely cautious in commenting on this much disputed field. I concede that during an earlier period (1916) I was less cautious and believed, on the basis of extensive studies of the literature, that it was justifiable to classify the clearly congenital form of homosexuality as an incipient form of intersexuality. At present I can no longer hold to this theory. What was discussed in the previous sections makes it very difficult to assign homosexuals of either sex a place in the series of intersexuals. Without pretending to be an expert in this field I should like to point out that what has been previously said about gynecomastia (an inherited change in the reactivity of the breast tissue to hormones) would also seem to be the most likely explanation for homosexuality, except that instead of the mammary gland *the brain* would be the end organ (italics added).

If the site of the divergent development in homosexuality is in the personality and ultimately, therefore, in the "mind" or in the brain or the nervous system, it becomes possible to study this deviation within the framework of the function of genetics in psychiatry, tracing the processes of interaction in the organism from its earliest origin and with its genetic potentialities.

Some observations made by Kinsey and his associates regarding the biological basis for the usual heterosexual choice, for example, may provoke speculation regarding the areas of defect in homosexuality. The factors facilitating heterosexual choice were listed as follows : (1) greater aggressiveness in the male with a tendency to avoid sexual behavior with another individual of the same level of aggressiveness; (2) greater ease of

intromission in heterosexual contact, with more of the "satisfactions which intromission may bring"; (3) olfactory and other anatomical and physiological characteristics differentiating the sexes; and (4) the conditioning effect of the "more frequently successful" heterosexual contacts.

In the heterosexual individual these factors would seem to require a normal rate of maturation of personality development, marked by the ability (1) to perceive and respond to biological sexual stimuli of a pleasurable nature; (2) to feel and recognize satisfaction and success; and (3) to utilize these experiences as integrating forces and guides to future action. A primary defect in perception or self-perception or response to pleasure may render an individual vulnerable to accidental or to family- or society-encouraged deviant behavior. Any vulnerability factors in homosexuality may well be of this nature, rather than what Rado calls "counter-fragments" of the opposite sex.

Other theories based on evolutionary considerations have been advanced by Hutchison and Comfort. The former suggested that the genotype responsible for homosexuality may operate on the rates and extent of the development of the neurophysiological mechanisms underlying the identification processes and other aspects of object relationship in infancy. Comfort considered the evolutionary significance of the time in which castration anxiety begins, a phenomenon that may protect immature male

animals from competitive harm between the onset of sexual maturity and the attainment of adequate size and strength. It was assumed that if this anxiety develops too strongly or too early, one reaction may be an avoidance of heterosexual behavior and a turning to homosexual behavior.

The plan used in observing those few one-egg twin pairs found with one clearly homosexual and one predominantly heterosexual partner has been referred to above. Psychoanalytic and other data on a pair of 30-year-old male twins classified as clinically discordant revealed important similarities, principally in psychological test findings. Both twins were reported as having shown marked sexual confusion and body-image distortion. Taking these results as a first approximation to the similar underlying personality characteristics expected in identical twins, the interpretation of the developmental material was focused on divergent patterns of experience. In this case, as well as in some others studied subsequently, an important factor seemed to be a difference in the twins' relationship with their mother. The preferred and ovcrprotected twin may have become frustrated in his heterosexual contacts and formed a poor masculine identification. It was assumed that the gene-influenced personality potentials were relatively vulnerable in both twins but led to homosexual symptom formation in only one. With this type of investigation aiming to pinpoint the crucial components of the developing character structure and the most sensitive periods at which they can be affected, it is obvious that many more cases must be studied

before any detailed interactional synthesis can be achieved.

Genetic Counseling

From the clinical point of view the final common pathway for the application of genetic knowledge to patients and their families is the responsible practice of genetic counseling— the provision of scientifically accurate guidance in connection with problems of marriage and parenthood. Changing attitudes and policies regarding fertility regulation, parenthood planning and population growth, and concerns with birth control, voluntary sterilization, genetic diagnosis by amniocentesis, abortion, and adoption procedures, have created an interest in and a demand for genetic information and for help in understanding that information.

The psychiatrist is involved in genetic counseling in two ways. First, he is best qualified to diagnose behavioral syndromes, as well as to interview family members and interpret records and laboratory tests. Second, he will have special skill in assessing the emotional aspects of the search for genetic information, the motivations, rationalizations, and defenses of the persons coming for help, and the impact of the information provided. Many persons accept misinformation and superstition if it is in accordance with their wishes or fears. Some couples look for reasons to avoid marriage and parenthood, while others who have had an affected child seek to alleviate their shame or guilt. Marital problems may arise, such as hostility and sexual inhibition. Considered as a psychotherapeutic procedure, genetic counseling presents,

therefore, a growing need for community mental health resources staffed by professional persons trained in modern genetic research methods, able to empathize with persons in need of guidance, and equipped with a sense of public responsibility. With proper concern the growing body of scientific and conceptual advances in genetics may be turned to human benefit, and psychiatrists may participate in the social planning that lies ahead as well as discharge their duty to foster responsible parenthood and genuinely healthy development in the families under their care.

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Notes

[1] Subsequent investigations revealed that satellites are carried by all the acrocentric chromosomes, except the Y, although they cannot always be seen; therefore, the use of satellites to distinguish between acrocentric chromosomes is probably not reliable.