Symposium on Inborn Errors of Metabolism

Mechanisms in Genetic Diseases of Man*

VICTOR A. MCKUSICK, M.D.
Baltimore, Maryland

CURRENTLY, the genetic questions of most interest and importance to the clinician are those that concern mechanisms in diseases of primarily genic causation, the pathologic physiology of genetic disease. Three interrelated questions are involved: What is the "basic defect,"† that is, the deviation from the usual, responsible ultimately for the observed manifestation(s)? What is the *modus operandi* of the basic defect,† that is, what intermediate steps or links are involved in the production of the observed manifestation(s)? What factors account for the variations in severity of clinical expression and, in some instances, for failure of the disease to develop at all despite the presence of the appropriate mutant gene?

The reorientation of interest in genetic disease, as in the case of all hereditary traits, is indicated by the apt analogy used by Snyder [3] who, in surveying the status of human genetics at the mid-century, wrote as follows: "In the early days of the study of genetics, the geneticist was content to establish the correlation between the gene in the chromosome and the characteristic in the individual, without raising much question as to the chain of events which connected the two. The attitude was very much like that of the traveler who boards the Miami train in New York confident that he will step out at the Miami station, but actually knowing very little about the physico-chemical principles of the Diesel engine or the intricacies of the switching and signaling systems that will get him there.

Today, however, the question of genic action in the development of finished characters is uppermost in the minds of geneticists, and biochemical genetics is leading the attack on this front."

Obviously there are other matters of considerable importance to medical genetics. These include (1) devising methods for recognizing heterozygous carriers of recessively inherited disease;‡ (2) mapping the chromosomes, that is, identifying markers on chromosomes so that the linkage of disease traits can be used to predict the genetic state of a given individual in a given family in respect to a given disease; (3) calculation of risks for bearing affected children or of getting grave complications, if affected—for use in genetic counseling which presently is at best difficult; and (4) study of factors influencing mutation rate. From both the therapeutic and

† The adjective "basic" as used in this connection is a relative term. With one possible exception the precise derangement of the functionally inadequate molecule has in no instance been described. In familial periodic paralysis the demonstration of a loss of potassium from the serum to the muscle and in *adynamia episodica hereditaria* [1] a movement of potassium in the opposite direction has provided the first approximation to an explanation of these two hereditary states. However, there are obviously much more basic mechanisms involved. In osteogenesis imperfecta pin-pointing the defect to collagen was an important step. However, it is likely that even more precise identification of the biochemical aberration will be soon forthcoming. In sickle cell anemia an important beginning in the description of the exact structural peculiarity of the molecule of sickle hemoglobin has been made [2].

‡ For example, Hsia [4] has shown that presumably heterozygous parents of patients with the recessively inherited trait, phenylketonuria, have a mild or incomplete defect in the conversion of phenylalanine to tyrosine as revealed by phenylalanine tolerance tests. Similarly in diabetes insipidus, a defect in urinary concentrating power is identifiable in the presumably heterozygous parents [5].

* From the Department of Medicine, The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital, Baltimore 5, Md.

the preventive point of view, these questions are not as important to the clinician, that is, to the physician concerned with the care of the individual patient, although they are matters of major concern to the field of public health.

In general, the main reasons for the importance of elucidating mechanisms might be listed as two. First, it is evident that treatment and prevention of disease in the individual patient must rest on a knowledge of mechanisms. This is a well accepted principle, which has unfortunately had thus far all too little confirmation in practice. It is a principle tacitly acknowledged by fund-granting agencies and special foundations for the study of specific heritable diseases. For example, sizable amounts of money are being spent to discover the "cause" of muscular dystrophy. It is, however, not the cause that is sought. The cause has long been known; the cause is a mutant gene, or rather, mutant genes, since a different gene is presumably responsible for each of the distinct types of hereditary muscular dystrophy. In actuality, what is sought are the mechanisms, the "basic defect," the modifying factors.

As indicated in this symposium, in phenylketonuria and in Wilson's hepatolenticular degeneration an intimate knowledge of mechanisms may permit effective treatment and prophylaxis in the not distant future. The simple expedient of withdrawing milk from the diet "cures" galactosemia. Furthermore, if the physician knew why the manifestations of genetic disease do not occur in some persons who carry the gene (why, as the geneticist puts it, the penetrance of the factor is reduced), if he knew why manifestations are negligibly mild in some persons (who, in the genetic jargon, display a low level of expressivity for the trait), then he might be able to mimic nature and influence the disease similarly by one maneuver or another. In hemochromatosis the female is partially protected from the disease through loss of blood and iron in the menses. Repeated venosections mimicking the physiologic process is effective treatment of the disease.

A second reason for the importance of studying genetic mechanisms is derived from the contribution to general biologic knowledge which can be made thereby. Agriculture and medicine are the two major divisions of applied biology. Probably in no connection does the physician have more frequent occasion to be reminded that he is basically a biologist than in relation to problems of inheritance. The relationship of medical genetics to general biology and its subdivisions is a two-way street. That medical genetics has much to learn from the biologic disciplines is obvious. Not so clearly recognized is the fact that clinical and allied investigation of genetic diseases can provide worth while and often otherwise unobtainable information about normal biologic processes. Sir Archibald E. Garrod, the acknowledged founder of biochemical genetics in man, enunciated this principle, illustrated and corroborated it by his own work, and further emphasized it [*6*] by the following quotation from a letter written by William Harvey in 1657, a few weeks before his death exactly 300 years ago:

"Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of Nature by careful investigation of cases of rarer forms of disease. For it has been found, in almost all things, that what they contain of useful or applicable nature is hardly perceived unless we are deprived of them, or they become deranged in some way."

The principle spelled out by Harvey and Garrod is perhaps nowhere better exemplified than in the case of the defects of the clotting mechanism. Eight or nine specific defects have been identified. These correspond to eight or nine specific essential factors in blood clotting which would be unknown were it not that patients have turned up with an hereditary deficiency of each. Whatever the field in which basic mechanisms are sought, hereditary perversions of the normal mechanisms should be studied: hereditary anomalies of renal tubular function should be helpful to the renal physiologist; hereditary gastrointestinal absorptive abnormalities to the gastroenterologist; inborn deviations in the function of endocrine glands to the endocrinologist.*

The search for the common denominator responsible for the diverse manifestations of hereditary syndromes is likely to result in new information of general biologic importance. It is certain to point up areas of ignorance. For example, investigation of fibrocystic disease of

* The work of Stanbury [*83*], demonstrating a different enzymatic defect in each of several varieties of goitrous cretinism, serves to illustrate this point.

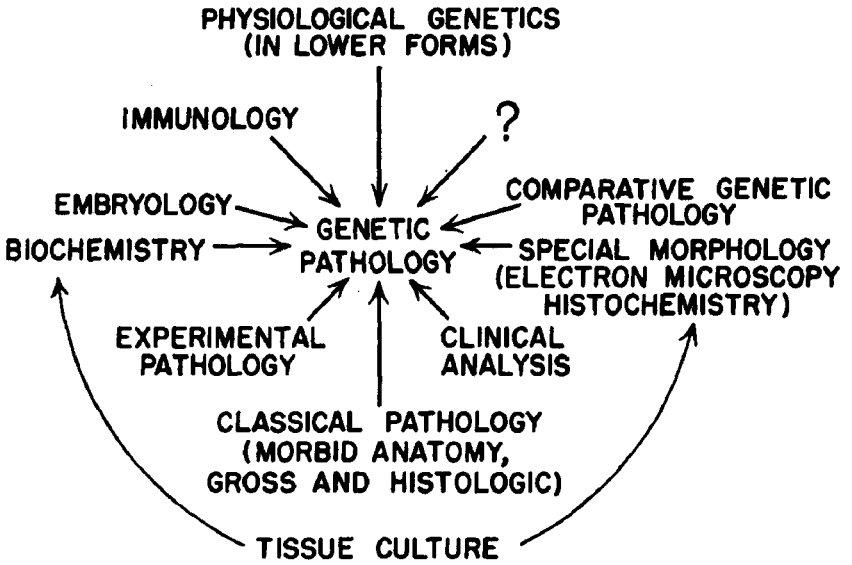

FIG. 1.

the pancreas and the manifold features not well indicated by this usual name of the syndrome—meconium ileus, biliary cirrhosis, bronchiectasis, pulmonary emphysema and fibrosis, "asymptomatic" changes in sweat and saliva—is likely to result in an increased knowledge of exocrine glands. "This type of thinking [relating diverse components of a syndrome] is bound to be profitable, if care is taken to distinguish hypothesis from proven fact, and to follow up promising hypotheses with pertinent evidence, observational and experimental" [7]. Jonathan Hutchinson, an indefatigable describer of syndromes, wrote: "We must analyse and seek to interpret, partnerships in disease" [*8*]. The blueprints for the analysis of mechanisms in hereditary diseases—the treasure maps, as it were—are the "pedigree of causes" diagrams which often begin to look a bit like the "flow chart" of a Rube Goldberg apparatus but which attempt to relate all manifestations of a given disorder back to a "basic" defect. The premises underlying such charts are (1) that all manifestations of a given syndrome are ultimately based on the action of a single gene (and are not dependent, for example, on gene linkage or some other mechanism), and (2) that "one-gene-one-function," if not a fundamental law of biology, is at least a satisfactory approximation. This is not the place to review the evidence for these well-founded tenets.

GENETIC PATHOLOGY

The problems under discussion here—problems in gene action—are subjects for investigation in the division of genetics called physiological genetics. Admittedly the whole category of hereditary disease-states merges imperceptibly at the edges into groups of "conditions" which if not considered entirely "normal" can scarcely be construed as diseases. I have in mind structural deviations such as polydactylism or accessory nipples. Nonetheless, physiological genetics seems an improper designation for this field of study when the trait requiring "explanation" is a disease. Genetic pathology seems more appropriate.

As is graphically represented in the accompanying diagram (Fig. 1) many disciplines have contributions to make to the field of genetic pathology. Furthermore, as mentioned earlier, feedback phenomena certainly occur. The question mark on the diagram is to indicate that it is entirely probable that important assistance in the solution of problems of genetic pathology may come from unexpected sources. We will comment on a few of the contributing areas specifically mentioned.

The availability of animals suffering from a genetic disease which is similar or possibly identical to human disease (comparative genetic pathology) should be helpful. Recently, for example, intense interest—and one might say optimism—has been stimulated by the report [*9*], from the Jackson Memorial Laboratory at Bar Harbor, of a mutation in mice which results in a disease resembling progressive muscular dystrophy of man in all important respects. The disease in mice seemingly identical with hereditary spherocytosis of man should give useful

TABLE I

Disorder	Animal	Mode of Inheritance	Studied by*
Achondroplasia	Chick	Autosomal recessive	Lamoreux [29]
	Rabbit	Autosomal recessive	Pearce, Brown [30]
	Cattle	.....	Crew [31]
Albinism	Many birds and mammals	Autosomal recessive sex-linked recessive	Pearson et al. [32]
Anemia, ? type	Mouse	Autosomal recessive	Gowen, Gay [33]
Anemia, spherocytic hemolytic	Mouse	Autosomal recessive	Motulsky et al. [10, 87]
Anophthalmos	Mouse	.....	Chase, Chase [34]
Cystinuria	Dog	.....	Crane, Turner [35]
Dwarfism, ateliotic	Cattle, etc.	Autosomal recessive	Mead et al. [36]
Dwarfism, pituitary	Mouse	.....	Francis [37]
Ectopia lentis and cataract	Cattle	Autosomal recessive	Gregory et al. [38]
Hare-lip, cleft palate	Mouse	.....	Reed [39]
Hemophilia	Dog	Autosomal recessive	Hutt et al. [40]
Hypoglycemia	Mouse	Autosomal recessive	Cammidge, Howard [41]
Jaundice, hereditary	Rat	.....	Malloy, Lowenstein [42]
Myotonia congenita	Goat	.....	Kolb [43]
Obesity	Mouse	Autosomal recessive	Mayer [44]
Osteogenesis imperfecta (anosteoplasia congenita)	Cattle	.....	Inderbitzen [45]
Pelger anomaly of leucocyte	Rabbit	Autosomal recessive†	Nachtscheim [46]
Porphyria	Cattle	Autosomal recessive	Fourie [47]
Retinal degeneration	Rat	.....	Bourne et al. [48]
Syringomyelia	Rabbit	.....	Ostertag [49]

* —usually only reference to recent study given.
† —lethal homozygote.

information [10]. Table I presents a few of the animal counterparts of human disease which have been described to date. Surveys of the genetic traits which have been identified in domestic animals are available [11–21,84].

The herditary jaundice in the rat, described by Malloy and Lowenstein [42], has been shown to be due to defective conjugation of bilirubin to bilirubin glucuronide [85]. Calkins [86] has under study a disorder in French poodles which resembles osteogenesis imperfecta in man.

Tissue culture is potentially useful to genetic pathology in at least three ways. (1) Tissue culture can provide the biochemist with the pure cultures of cells which delight his heart and simplify his tasks. (2) It can help settle the question of whether a given disease is a primary and autonomous abnormality of one tissue or, alternatively, whether the pathologic changes observed in a given tissue are merely secondary to a remote metabolic, endocrine or other disorder. For instance, in muscular dystrophy the work of Geiger and Garvin [22] seems to have established that the primary defect, in the variety of the disease studied, resides in the muscle cell itself. In infantile genetic agranulocytosis, a recessively inherited condition identified in an isolate of northern Sweden [23], short-term cell culture, using bone marrow from affected subjects, has indicated that the basic defect is a disturbance of white blood cell maturation and that the defect can be corrected by addition of cysteine to the culture media. The last is a preview of another potential contribution of tissue culture. (3) The possibility of influencing the expression of the gene through changes in environmental factors can be explored *in vitro*. The experiments of Puck [24–26] illustrate what methodological progress has already been made in the application to mammalian cells growing in tissue culture of the same technics which have been used in studying biochemical genetics in bacteria and in molds, such as the classic Neurospora.

Experimental pathology can contribute to genetic pathology by the production of phenocopies, that is, facsimiles of the genetic disorder. The term "phenocopy" is Goldschmidt's [27]. Congenital malformations which in man are genetically determined can be closely simulated, in the experimental animal, by a large variety of maneuvers [28]. The toxin for connective tissue contained in the seed of the garden sweet pea (*Lathyrus odoratus*) produces kyphoscoliosis,

hernia and dissecting aneurysm of the aorta in rats—a syndrome resembling the gene-determined Marfan syndrome of man.

It is unnecessary to cite examples of the numerous contributions of the biochemists to genetic pathology, since the papers of this symposium provide adequate illustration. It is attractive to speculate that all genetic pathology will ultimately be reduced to biochemical terms.

There are a large number of hereditary states of developmental-morphologic type in which there is virtually no knowledge of the basic mechanism. Merely to select a few from among many, one might mention multiple exostoses, tuberose sclerosis, Osler-Rendu-Weber telangiectasia, Ollier's enchondromatosis, retinoblastoma, cystic disease of the kidneys, hypertrophic pyloric stenosis, the dysplasia of the acetabulum which is the structural substrate of congenital dislocation of the hip, brachyphalangy, achondroplasia. One suspects that embryology may have something to offer in the study of these disorders, especially in conjunction with biochemical and other technics.

Embryology has thus far contributed relatively little to a knowledge of mechanisms in genetic disease, mainly because the field has been handicapped by great technical difficulties. Embryogenesis is difficult to study in man. A comparison of embryogenesis in lower animals with special reference to specific malformations is likely to be helpful, as the experience [*50*] with cleft palate would appear to indicate. Chemical embryology, which attempts to define in chemical terms the phenomena of experimental embryology, can be expected to establish increasingly close connections with genetics.

Immunology, by defining differences between body proteins, should have useful contributions to make [*51*]. The globins of some abnormal hemoglobins are antigenically distinct [*52*]. Although there are other characteristics which more simply distinguish these particular abnormal proteins, there may be some disorders in which immunologic technics will be necessary.

The increasing importance of genetic disease, as other major categories such as nutritional and infectious are controlled, will necessitate a reorientation of educational curriculums not only for persons whose ambition it is to do research in the field of genetic pathology, but also for the medical student in general. Genetics and embryology will occupy an important place in such a reoriented medical curriculum.

THE COMPLEXITIES OF GENETIC PATHOLOGY

The complexities with which any analysis of genic action in man must cope become quickly evident. To begin with, man probably has 23* pairs of chromosomes, each possibly with as many as 5,000 genes. In the second place, there is rarely an immediate relationship between gene and phene. There is usually a chain (or better, a net) of reactions, each link of which is gene-controlled. Therefore, mutation in any one of several different genes may result in the same ultimate phenotype. Stern [*54*] uses the analogy to a stalled car: In this case the phene, stalling, can be due to a number of causes. Actually, as in the case of stalling, ancillary symptoms and the mode of inheritance may narrow down the possibilities as to the nature of the biochemical defect. Furthermore, the concept of alternative metabolic pathways [*56*] and that of competitive pathways open up many possibilities as to (1) variability in expression of a trait because of partial compensation through detour metabolic routes which may be open to varying degrees in different persons depending on other gene differences, and (2) production of the same phene by a number of different genes. A number of examples can be cited to illustrate the fact that many genes may have roughly similar effects: there appears to be more than one genetic variety of the adrenogenital syndrome [*57*]; although, as was pointed out to Garrod by Bateson soon after the rediscovery of Mendel's work, most cases of alcaptonuria demonstrate the pedigree characteristics of a recessive trait, there are occasional pedigrees [*58*] in which dominant inheritance is displayed and a slightly different biochemical lesion is possible although unproved. There is more than one mode of inheritance for albinism and for retinitis pigmentosa; there is probably a different gene responsible for each.

Parenthetically, however, it should be emphasized that current theories of dominance and recessivity [*59*] do not necessarily require one to conclude that a difference in mode of autosomal (non-sex-linked) inheritance necessarily indicates that a different gene is responsible for the given trait or a different link in the biochemical chain is defective, although probably as a rule such is the case. Further example: although con-

* Until recent studies [*53*] revealed the true situation, it has been thought and taught that man has 24 pairs of chromosomes.

genital spherocytic anemia is inherited as a dominant in man and as a recessive in the strain of mice studied by Motulsky [*87*], the difference in mode of inheritance is explicable on other grounds than different defect; the pathophysiology of the syndrome defect appears to be identical in the two species. One would expect, however, that a trait inherited in a sex-linked manner would be biochemically distinct from a phenotypically identical trait inherited autosomally in the same species.

The phenic consequences of genic action may be so remote from the primary operation of the gene that one may end up with the association of manifestations which are difficult to relate to each other. Such is the case in many hereditary syndromes. Elsewhere [*60*] the evidence for a single-gene basis of hereditary syndromes in man is presented. Accepting this seemingly adequately established hypothesis as fact, one is left with syndromes—melanin spots of the buccal mucosa, lips and digits associated with garden-variety adenomatous polyps of the gastrointestinal tract [*61*]; the syndrome of colonic polyps, osteomata and soft tissue tumors [*62*]; polycystic kidneys and intracranial aneurysm [*63*]; the association of obesity, retinitis pigmentosa, polydactylism, mental retardation and sexual infantilism in the Lawrence-Moon-Biedl syndrome;* retinitis pigmentosa with the Fanconi syndrome [*64*]; total color blindness with otosclerosis [*65*]; muscular dystrophy with baldness, myotonia, cataracts, testicular atrophy in Steinert's disease; and so on—in none of which current knowledge permits an understanding of the interrelationship of the component manifestations. Genuine pleiotropism, that is, multiple primary actions of a single gene, once considered a possible mechanism for the syndromal association of diverse phenes, now appears unlikely. Evidence from various sources suggests that each gene has but one primary action, the ramifications of which may, however, be exceedingly widespread. It is in the type of syndrome just cited by way of illustration that an analysis of the common denominator should reveal significant biologic information.

The complex interrelationships of genes can be looked upon as intracellular or intraorganismal ecology. The introduction of a goat [*55*] onto an oceanic island is likely to produce widespread effects; the relation of some of the consequences to the original change and to each other may not be immediately evident, nor may it be easy to sleuth out the basic defect responsible for radical changes in the physiognomy, fauna and flora of the island. The ecologic effects of the introduction of a mutant gene into a new genetic environment are similarly intricate.

Except for sex, the factors modifying the "expressivity" of mutant genes in man are largely unknown. Furthermore, in many instances the reason for sex differences* in the grade and frequency of inherited traits is poorly understood. In some situations the sex differences in expression are seemingly a result of the different hormonal environments. Hereditary hypercholesterolemia would appear to be an example. In general, women before the menopause have an advantage over men as to fat metabolism and consequently as to the incidence and severity of atherosclerosis. Castration of the female or the onset of menopause returns the female essentially to the position of the male in this regard. That estrogens are responsible for the sex differences in expression of the gene or genes responsible is a conclusion supported by experimental and clinical observations on the effects of administered estrogens. The effects of the gene for baldness may be potentiated by androgens such that heterozygous men are bald but women are bald only if homozygous for the trait (or heterozygous with a masculinizing tumor). In other instances differences in physiologic function, specifically the occurrence of menstruation and pregnancy in the female, account for the observed sex differences. For example, in hemochromatosis, the periodic loss of blood (and iron) in the menses provides a partially effective safety valve against development of the disease in women [*66*]. Physiologic differences in gametogenesis may be responsible for male-female differences in gout. Stetten [*67*] suggests that nucleoprotein metabolism associated with spermatogenesis is so much more active than that of oogenesis that the sex difference in expression of the gene for gout may be explicable on this

* The obesity and sexual infantilism may find explanation in a defect of nervous tissue which involves the hypothalamus and also involves the higher centers and retina, explaining mental deficiency and retinitis pigmentosa, respectively. The polydactylism is more obscure.

* Assumed in this discussion is that the sex difference is biological and not social or statistical. For example, rare biochemical defects, such as fructosuria, are sometimes apparently more frequent in men, probably only because more men than women are subjected to examination in connection with work, insurance and armed service.

basis. The *modus operandi* of the sex factor is unknown in many situations. Why does Marie-Strümpell spondylitis, which seems to be inherited as a dominant, occur in approximately 70 per cent of men with the gene but in only approximately 10 per cent of women? Why is hypertrophic pyloric stenosis of infants, quite clearly hereditary,* more frequent in males and, equally puzzling, in first-born males? Why is so-called congenital (actually hereditary) dislocation of the hip over five times more common in women [*69*]?

In general, the expression of a gene depends on the rest of the genetic makeup of the person and on factors of the environment, both intrauterine and extrauterine. The influence of the genetic milieu is sometimes observed in the Marfan syndrome: the characteristic skeletal proportions may be relatively unimpressive when the mutation occurs in pyknic stock. In the case of dominant conditions there is need for pedigree studies with analyses of the normal lines to determine the influence of various "normal" phenotypes on the expression of the mutant gene. To be decried is the usual practice in pedigree studies of concentrating on the side of the house through which the disease in question was inherited.

SOME PRINCIPLES OF GENETIC PATHOLOGY

Despite the complexities of genetic mechanisms a few principles have emerged; several of these have been outlined by Dent in the introduction to this symposium and are illustrated in the individual contributions. The following are also worthy of note:

The mechanism of genetically determined drug idiosyncracy has been identified in two instances. The first was the identification of the basis for susceptibility to hemolytic anemia from administration of certain agents [*70*]. It was found that the level of red cell glutathione is low and that the basic defect concerns glucose metabolism; specifically, glucose-6-phosphate dehydrogenase seems to be faulty [*71*]. The second is the susceptibility to prolonged, profound effects of succinyldicholine which is used as a muscle relaxant during anesthesia. The basis has been shown to be a deficiency of serum pseudocholinesterase, which under normal circumstances is responsible for the breakdown of the administered drug [*72*]. It is of note that in neither case would the genetic peculiarity become evident were it not for the administration of the drug. What is the basis for the not infrequently fatal idiosyncrasy of mongoloid idiots to agents of the atropine group? Genetic differences in susceptibility to infectious diseases such as tuberculosis [*73*] should eventually be explicable in terms analogous to these drug reactions [*74*]. Genetic differences in nutritional requirements and in susceptibility to allergens, thus far poorly understood, are further examples of the interplay of constitution and environment.

There are probably many hereditary diseases in which, in the last analysis, all the clinical manifestations stem from the fact that a given species of protein molecule is fabricated in a manner that places it at a functional disadvantage. This is what Pauling and his associates term "molecular disease" [*75,76*]. The best-studied example is sickle cell disease. Some subtle abnormality of the globin of hemoglobin [*2*] results in striking functional differences which are responsible for the manifestations of this disease. Abnormal protein synthesis is almost certainly at the basis of many diseases: abnormal fibrous proteins in heritable disorders of connective tissue,* abnormal contractile protein in muscular dystrophy,* and so on.

Furthermore, in diseases which have been discussed or referred to in this symposium and in which the basic mechanism is thought of as being an "absent" enzyme of intermediary metabolism, "absent" enzymes of specific functional significance as in the renal tubule, "absent" proteins with special function as in clotting or immunologic reactions, and the like, may all be somewhat artificial distinctions among members of a general group of conditions in which proteins are present, that is, normal quantitatively, but defective in some functional respect because of a structural peculiarity. It is entirely probable that in most if not all of the instances described the specific protein to which the defect is related is present but it has lost the earmarks by which we identify it. In the cases of many proteins, the enzymes for instance, function is the only criterion of identification. In this connection Pauling's concept of molecular disease is, as he

* Carter and Powell [*68*] made an extensive investigation which principally involved tracing infants who survived the Rammstedt operation 1920–1929 and who by the time of the study (published in 1954) had children of their own. Of 197 second-generation children, nine boys and one girl had had the Rammstedt operation!

* These are obviously speculations, the special license of the essayist.

maintains [*76*], of general significance. The possibilities for human variation and for disease on a genetic basis and through the agency of molecular changes are indicated by Pauling's statement that "there are of the order of 100,000 different kinds of proteins in the human body." One is impressed with the great importance of protein synthesis in genetic disease; the machinery for protein synthesis must be linked very closely to the gene itself.

In connection with the Seabright bantam cock, which has a comb with female characteristics despite the obvious virility of the bird, there has been defined a principle applicable in several areas of human genetic pathology: the defect in a disease which has the phenotypic pattern of a hormone deficiency may reside in the receptor organ which is genetically incompetent to respond to a normal amount of circulating hormone. Examples are represented by pseudohypoparathyroidism [*82*], nephrogenic diabetes insipidus, possibly ateliotic dwarfism.

The fascinating recent work on the pathogenesis of congenital spherocytic anemia [*77*] possibly illustrates a significant principle, namely, that it is possible to identify a biochemical basis for anomalous structure. It would have been easy a decade ago to accept this condition merely as a hereditary malformation of the erythrocyte (which in a sense it is) which renders it unusually fragile to osmotic and mechanical stress and susceptible to destruction in the spleen. It now seems likely that there is a defect in the glycolytic process which provides energy for maintenance of the integrity of the red cell stroma and membrane. Autohemolysis after trapping of red cells and depletion of substrate in the spleen is probably mainly responsible for the anemia. The biochemical basis for other structural abnormalities must be sought.

If not a principle of gene action, a useful concept is that implicit in the term *abiotrophy* invented by Gowers [*78*], who described the phenomenon in connection with certain neurologic disorders: that tissues of the central nervous system are clinically normal and probably histologically normal (by available methods of examination) in early life, but have a subtle innate weakness which results in their premature degeneration functionally and structurally. Several mechanisms for a picture of abiotrophy are possible. The mechanism to which the term is possibly most legitimately applied is that seemingly operative in the skin in pseudoxanthoma elasticum and in the aorta in the Marfan syndrome [*60*]. Both structures probably are at birth normal by all available criteria but do have a defect, probably of collagen in the first example, possibly of the elastic fiber in the second, which renders them liable to breakdown with the usual stress and strain. The skin of the flexural folds is first to show changes in pseudoxanthoma elasticum, whereas the ascending aorta which is subjected to maximal hemodynamic stress of particular types demonstrates the earliest and predominant changes in the Marfan syndrome. A mechanism for what might be called pseudoabiotrophy is the accumulation of an unidentified material which is toxic to a specific tissue or cell type. Until such time as the pathogenesis is worked out such a disorder might be misinterpreted as an abiotrophy. Wilson's hepatolenticular degeneration is an example of pseudoabiotrophy.

I think abiotrophy is a useful concept even if for no other reason than that it points up the fact that a disease can be primarily hereditary in etiology even though at birth it is not present by any current methods of detection applied to the individual. The concept can be a deterrent to progress if it is not appreciated that the basic defect *is* present at birth and will eventually probably be identifiable even in its preclinical state.

Another phenomenon concerning gene action is the conditioning of specific congenital malformations as the result of the presence during embryogenesis of a specific defect. Examples [*60*] seem to be provided in the Marfan syndrome and the Ehlers-Danlos syndrome, which appear to be specific defects of specific elements of connective tissue. However, in these syndromes certain congenital malformations occur with increased frequency and probably result from effects of the weakness of connective tissue at vital points in embryologic development.

A now familiar, though relatively recently discovered, general mechanism of genetic pathology concerns fetal-maternal interrelationships, specifically the immunologic effects of certain genetic differences between mother and fetus. Rh incompatibilities are the major known examples, but others, such as in the ABO series, are known and still others are probably as yet undiscovered.

In breast cancer of mice the milk factor which is responsible for an apparent hereditary nature behaves like a virus [*79*]. That a comparable

situation in man exists in the case of colonic polyps is suggested by the description of cytoplasmic inclusions which have morphologic characteristics of viral inclusion [*40,81*]. Admittedly these are not genetic diseases in the precise sense. Cytoplasmic inheritance is an alternative possibility raised by this finding of DNA-like material.

COMMENTS

Obviously, all diseases are influenced in at least some small part by genetic factors. Each sick person is a different, complex organization of genes who because of these differences has a particular susceptibility to a given disorder and a particular mode of reaction to disease. This is why we tell students there is no such thing as a "negative family history"— as absurd as recording "no spleen" in the normal physical examination. Genetic mechanisms in disease which are not primarily caused by a mutant gene are also important to elucidate, for example tuberculosis, as has already been mentioned.

Furthermore, just as heredity can influence diseases primarily of environmental origin, environment can influence genetic diseases. This fact is used in the treatment of genetic disorders. In coronary artery disease both a hereditary factor, in the form of peculiar fat metabolism, and diet, particularly increased fat ingestion, may be factors. Depending on its character, diet can favor or inhibit expression of the disease. It is difficult to know whether coronary artery disease should be classified as predominantly environmental or genetic, but the two certainly are not mutually exclusive.

I have attempted to show that, although the ultimate goal, and a reasonable one, is definition of the biochemical nature of genetic diseases, a general view of mechanisms, not confined to the biochemical aspects, in genetic diseases of man can and should be taken.

It has often seemed entertaining to imagine, Jules Verne style, bizarre diseases previously unknown. If one were to do this, imagining hereditary defects and basing the speculations on a sound knowledge of normal mechanisms, one could predict with considerable assurance that the imagined disease would at some time be encountered.

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