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New Goals and Perspectives in Human Genetics*

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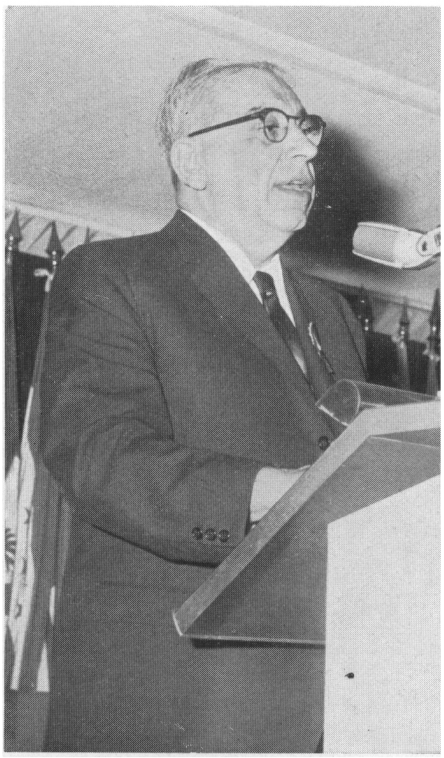

Standing here at the magnificent site of our Second International Conference (1961), I am only too glad to put behind me the obscure threat that cast a long shadow on my eagerly anticipated reunion with you and for a while placed it in the same wishful dream category as this Eternal City built by twins—this wondrous world of classic treasures and a free-flowing evolution toward new Heights of Renaissance in the annals of man. Under the circumstances, you will forgive my saying in all humility and with a full heart that the task of opening the scientific portion of this Conference is not only a great honor to me and my American coworkers and friends, but a source of deep personal gratification.

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My excitement is increased by the fact that during the five years since our First International Conference in Copenhagen (1956), enormous strides have been made, either directly or by feedback, in our steadily growing and by now fully recognized discipline of *Human Genetics*. While it is understandable that these remarkable gains should have lent us courage, imagination and self-assurance, they will prove even more valuable in the challenging years to come when solid ground will be needed for building new towers of scientific achievement.

At this moment we would do well to pause and consider that auspicious developments of such magnitude call for certain readjustments in our *goals and perspectives*. It may not really matter whether it is in the organization of truly integrated, multidisciplinary *genetic training facilities,* or in the planning of sufficiently broad and penetrating *research programs,* or in the molding of a scientifically unified and humanistically progressive professional attitude imbued with a *social-minded sense of responsibility,* that a realistic reappraisal is considered by our rank and file workers to be most urgently needed. What we do have to remember is that the notable advances of our discipline in the current quinquennium have taken place against a backdrop of disproportionate population growth, creeping social unrest, haphazard cultural change, and a whimsical preoccupation with our steadily expanding universe and its implied global dangers, psychological as well as biological.

Regardless of whether such universal pitfalls are approached from a political, religious or strictly scientific viewpoint, they are known to be rooted in various imperfections of the human species as a whole and of its smallest formative units, *the family*. Hence, no matter what our everydav activity at home, and our particular subspecialty within the clinical or biological sciences, we have come to this Conference with the firm conviction that in coping with these worldwide population problems, some unique rewards can be derived from exploring the *microcosmic structure* of our immediate human world, the matrix of all continuous life processes. The geneticist's main function in this never-ceasing struggle for survival is to cast more and more light on the mysterious ways in which human life originates, is fulfilled, and may be perpetuated toward an harmonious state of "freedom of mind" (23). He is expected to act as expert guardian of what is solid and good in man's genetic heritage, and to protect diligently and with

forsesight born of knowledge and a genuine humanitarian outlook what is capable of further improvement through intelligent use of modern technical and scientific principles.

In line with genetic theory, and among many other human values, all health and behavior potentials may be safely assumed to rest upon the cytochemical properties of well-integrated gene units in the nucleus of cells endowed with the ability to store a vast amount of hereditary information (17). Inseparable from man's evolutional advance, his adaptive strength, and his hope for continuous well-being and posterity, it is the intracellular dynamics of this *molecular life network* of the human being that we must learn to decode in all its essential ramifications. Unless we courageously take the lead in completing this vital task, other professional groups concerned with the health and family problems of modern societies cannot possibly be urged to risk reevaluating their position in relation to the untapped potentialities of genetically sound methods of research, guidance and education. Since a chronic lack of knowledge about gene-borne phenomena is easily rationalized, it does not lead to a perturbing state of mind for a great many people.

It is by no means certain whether, in 1961, old-time geneticists working on clinical and population problems in man still need any excuse for their notoriously slow progression from the era of vaguely formulated genealogical, ethnographic and statistical schemes to the precision of modern molecular biology. If they do, they may point to the depleted ranks of their adolescent discipline, their limited support, and the plethora of technical obstacles strewn along the way to well-founded concepts of meticulously interacting microcomponents of living cells which can be cultured, labeled and manipulated (16, 17). This non-projective line of defense seems more realistic than the outdated and piously dichotomizing scapegoat argument that progress in human genetics was so needlessly delayed by ideologically conceived and eugenically motivated crosscurrents that it may be said to have been "impeded less by lack of means than by lack of a clear scientific goal" (6).

In accord with L. C. Dunn's reminder in his recent Atlantic City address (6), it is important to emphasize the harmonious relations that should exist between sound genetic knowledge and prudently directed medical research, on the one hand, and the burning desire, on the other, to apply them constructively to the welfare of human

societies. Nevertheless, it is far too pessimistic to expect the joint forces of human genetics, eugenics and public health medicine to fall into a cunning trap whenever they venture too far from what has been neatly referred to as " the logical unity of genetics "; that is, an approved pattern of conduct and interests conforming to the usually benevolent principles of a matriarchal system in an ivory-tower atmosphere. As Slater (25) put it in his well-balanced Galton Lecture delivered last year, we may insist that " social efforts, which are not supported by the weight of the evidence and by a consensus of informed opinion, should be held in reserve ... but we must have some sense of proportion ... as we can make a fetish of the heterozygote just as Galton made a fetish of the extreme deviant ".

It is evidenced by the history of the human sciences that no one group, however status-seeking or status-quo-bound, has had a monopoly over those emotional, moral and intellectual forces conferring resistance to the formulation of oversimplified schemes " when man himself is the object of inquiry " (6). By the same token, it is also a fact that no scientific discipline has been completely immune to abuse by fanatics, quacks and opportunists, especially in its earlier years of development. On the whole, we may be confident that despite some exposure to sentimentalized eugenic ideas, the vast majority of properly trained workers in genetic guidance centers for distressed families will remain on safe ground as long as they value and adopt what in medicine has always been known as "*the professional spirit* " (20).

Defined by American Medical Association president, Leonard Larson, as a conglomeration of science and art, ethics and tradition, philosophy and compassion, this spiritual quality has been an indestructible force in medicine since ancient times. Characterized " by a thirst for knowledge and a striving for excellence in both scientific achievement and human relations ", and as unchangeable " as belief in freedom or love of humanity ", this spirit impels respect for the individual and " is shared by all people who value quality and truth, have concern for their fellow men, and are motivated by a sense of ethics and morality " (20).

Basically, then, aside from specific applications in matters of life and death within the province of medicine, this is the same spirit that makes professional workers in the public health field proudly aware of the part they have to play in the world around them. When applied

to eugenic problems, this spirit reflects what Weaver (29) referred to as "the moral un-neutrality of science" and what Wiggam (30) called the "last great appeal to the moral and religious passions of mankind". Apparently, pure eugenic thought may have been too costly an ideal for man to cope with, but, in the words of Wiggam, it is "nothing short of man taking his evolution into his own hands and shaping his own organic destiny to larger, happier and more fruitful ends" (30). Thus Hippocratic and eugenic brands of philosophy join hands in faithful unity.

Even so, it is regrettable that the earlier developmental stages in the history of both human genetics and eugenic family counseling were rather sluggish. With life then at a leisurely pace and in the absence of severe threats to the survival of human culture and ingenuity, it took about 100 years to explain Darwin's theory of natural selection, or the results of Mendel's definitive breeding experiments, or Weismann's imaginative concept of the heredity-borne continuity of the germ plasm in terms of minute nucleic acid units forming a precisely arranged system of chromosomes and genes. Almost as much time was needed for bridging the gap between Virchow's politically molded view of the human organism as a "democratic federation of cells blessed with liberty, equality and a more or less amorphous protoplasm" and the fabulous double-helix model of a DNA molecule functioning as the transferring agent of the genetic code (17).

Of course, it is truly remarkable as Dunn (6) has pointed out, that thanks to the pioneer work of brilliant men like Bridges, Goldschmidt, Muller and Sturtevant, the general architecture of the genetic material was largely known by 1915. Also, some particulary important implications of genetics for the analysis of gene action in man were foreseen by Garrod (9) in 1908, and the primary generalization of population genetics was independently formulated by Hardy, Pearson and Weinberg around 1908. Nevertheless, even if "we date the definitive elucidations of the physical basis of heredity as late as from the publication of Morgan's *Theory of the Gene* in 1926" (6), the fact remains that progress in augmenting genetic knowledge in man was extremely tardy in the first half of this century.

Similarly, a snail's pace prevailed in the group of pathological conditions now identified as the result of gross chromosomal disarrangements or gene-specific enzyme deficiencies (16). The stony path

from the halfway mark where the various phenotypic expressions of a mutation in the chromosome material are recognized as a clinical entity to that genetic peak station where the mutant gene effect is structurally or chemically elucidated, is well illustrated by two clearly delineated syndromes of general interest, congenital acromicria and abnormal sexual differentiation, both of which present little diagnostic difficulty at the clinical end-point in the patient's phenotype.

In the "*trisomy 21 anomaly*" (1), described by Langdown Down under the misleading name of "mongolian idiocy" in 1866, it took all of 93 years to knit the organic pattern between the two major points of interest. Despite very suggestive evidence for a genetic origin of the anomaly, derived especially from twin data (2, 13), it was not until the earlier part of 1959 in France (21), and later that year in England and Sweden (11, 4), that acromicric defects were shown to arise from non-disjunction of chromosome 21. Shortly afterwards, some cases were found to be associated with a translocation or deletion of a major portion of this chromosome, but the principal objective, namely, that of clarifying the basic etiology of this trisomic condition, has not yet been attained. In Lejeune's opinion (22), acromicric patients have multiple defects in tryptophan metabolism which impair their intellectual capacity, probably through a reduced serotonin content in the brain. Nevertheless, what remains to be done is to determine as soon as possible how to control either the development or the clinical consequences of this chromosomal disarrangement.

It may be that not all the therapeutic or preventive aspects of this ultimate requirement can be met in the immediate future. However, we heartily extend to our friends and colleagues working in this intricate cytogenetic field our warmest congratulations on their valuable contributions to the successful advance of our discipline. The unmistakable lessons conveyed by their brilliant discovery will be of great help not only in seeking methods of correcting this severe defect, but also in family counseling and the mapping of human chromosomes. No one can possibly deny that both impetus and direction have thus been given to further investigative and therapeutic research programs within the province of human genetics.

Perhaps even more dramatic has been the recent success in exploring the cytogenetics of *disturbed sexual development,* if only because it was accomplished in a shorter space of time. It is understandable that sex, from the medical and psychological viewpoints, was largely

regarded as a function that develops in infancy, depends on hormones, and is apt to be thwarted, tabooed and repressed (17). Even on the biological side, however, it was not associated with chromosomes until the early part of the century. It was in 1905 that Henking's "X body," discovered in 1891 in the spermatogenesis process of certain insects, was found by Wilson to be a chromosome concerned with sex determination, while the male determining role of the small Y-chromosome was not uncovered until 1959 (8, 26). Prior to this discovery, sex determination was thought of either as the result of opposing male and female determiners (in line with the genic balance theory as applied to sex), or as an expression of two genetically different developmental systems. Only since 1959 has it been reasonably certain that the presence of a Y-chromosome makes a fertilized ovum develop into a male and its absence causes the ovum to develop into a female.

With all my fingers crossed, may I add that I hope this rather definite statement taken from Curt Stern (26) will at least stand until the later sessions of this Conference. If the formulation is to be revised, I promise to do it on the way home.

Another outstanding achievement enhancing our understanding of a great variety of organic sex disturbances was the development in 1949 of a simple staining technique whereby *sex chromatin* could be shown to be present in female cells and absent in male cells (3). While the cells of normal males are chromatin-negative, having neither a Barr body nor a drumstick in their polymorphonuclear leucocytes, a normal female with two X-chromosomes is chromatin-positive. Possession of more than two X-chromosomes raises the number of stainable Barr bodies in such a way that there is always one sex chromatin patch less than there are X-chromosomes (5).

As it is, the *total list* of sexual disorders, mental defects and inborn metabolic errors, which within a few years have been identified at least in part with these and other laboratory procedures, is impressive, but it is likely to be extended in rapid succession, probaly even during the proceedings of this meeting. Representing a veritable saga of how much can be accomplished by a few laboratories working with proper tools and directives, this list includes, in addition to the trisomy 21 anomaly, and among the autosomal forms of chromosomal disarrangement, such crippling malformations with or without marked mental defect as anophthalmia, Sturge-Weber's syndrome and a variety

of gross skeletal abnormalities; also, among the nearly 300 gene-controlled disease entities with a more or less known metabolic error as the basic cause (10), such potentially treatable conditions as galactosemia, drug idiosyncrasy and glycogen storage disease; and among the now appropriately classified sex disturbances, especially the three main categories of Turner's syndrome, the superfemales with three or four X-chromosomes, and the familiar syndrome described by Klinefelter, Reifenstein and Albright in 1942 as being distinguished by small testes, gynecomastia and elevated urinary excretion of gonadotrophins, and two years later—under its original name of "primary eunuchoidism "— attributed by us, with some daring, to an aberration in the sex-chromosome complement (18). There is definite hope, too, that in the next batch of pathological conditions that will yield to refined cytochemical scrutiny there will be such menacing and life-shortening disorders as hypertensive disease, schizophrenia, Huntington's chorea, and certain forms of cancer (17).

With a multitude of promising technical research reports to be presented in the subsequent sessions of this meeting, we are pleasantly alerted to the prospect of another real breakthrough that may be initiated by some of them, comparable to the one staged by Tjio and Levan (27) at our First Conference in Copenhagen. For obvious reasons, however, scientific breakthroughs in all fields tend to occur where they are least expected. Hence, it would be presumptious on my part, in an introductory address, and a physical impossibility to boot, to strive for completeness in this general progress report or offer further specific details.

Instead, it would seem a propitious place here to emphasize once again the stimulating and solidifying effect which recent conceptual and procedural changes in our discipline have had and are bound to have even more strongly in the future on the development, maturation and unity of the one field of interest we all have in common, *human genetics*. That we have reached such a broad and firmly established platform at all is adequate proof of our existential rights, our intradisciplinary hybrid vigor, and our legitimate insistence upon a place in the sun along with the basic and applied human sciences. However, what may still be somewhat improved upon in a discipline which is rooted in the complexities of experimental, statistical and biochemical genetics, but permeates into every medical and behavioral specialty and gives coherence to all the biological and social sciences,

is a feeling of *professional solidarity and pride,* generated by a social-minded attitude and freed from the residual tensions of both inter- and intra-disciplinary sibling rivalries (12, 13).

Human genetics cannot afford to be a pure science confined to the laboratory and restricted to theoretical deduction and timid extrapolation. In action, it is a science of genetics applied to people, to benefit people, and to be understood by people for their own good and that of their progeny. In our conforming world, it is typical of human beings in general that they trust the word of authority, regardless of the scientific validity of that word (24). For the layman, the authority of human genetics is dispensed by physicians, educators, social workers and public health officials, whether or not they are adequately informed.

With the emergence of a strong and widely trusted discipline of human genetics, we must be ready to use our various scientific skills in the area of research and, at the same time, meet our responsibilities as teachers and full-fledged members of the public health profession. We need the scientist as well as the medical practitioner, the psychologist as well as the statistician, the specialist as well as the family physician, provided they are willing to undergo adequate genetic training, at least in some sector of specialized counseling work (12, 14). Although some of our research workers tend to lean toward academic skepticism and professional superspecialization (often expressed in the form of a pessimistic preference for the tools rather than the prospective beneficiaries of genetic investigation), it would be unfair to assume that a well-trained student of human genetics cannot at the same time be scientifically detached, professionally competent and social-minded. Optimism in this regard is encouraged by the history of biology and the records of enlightened humanitarianism made by scores of great biologists (7, 13).

The main obstacle to the realization of the *privileged position* of human genetics among the biological and medical sciences has been the scarcity of diversified training programs in which future specialists in human genetics are taught how to broaden their frame of reference from genetic to human problems. They have to be told somewhere why they should feel responsible for a general comprehension of the fact that mankind as a whole must learn how to *survive* safely. Only then can any real benefits be derived from the multitude of important

contributions that human genetics is able to make to our scientific schemes and therapeutic programs.

Professional geneticists, in dealing with matters of general health education, have to be trained in how to encourage a person's feeling of responsibility for himself, without losing sight of the all-important concept that a well-planned family is indispensable as a biological, social and cultural unit. As members of a health service team, they are expected to empathize with persons in need of guidance and, certainly, they should always be mindful of the age-old medical principle of *nil nocere* (14, 15). A person in whom fears of a crippling or fatal disease are instilled or aggravated by thoughtless or strenuously realistic remarks of an inexperienced investigator is likely to misinterpret even the most logical advice and may become as distressed and debilitated as if he were actually afflicted with the disease he dreads. Obviously, it is just as inappropriate for a geneticist to create anxiety in a research subject, or to withhold tension-relieving support from undecided, perplexed individuals when it lies within his power to provide such help in a counseling situation, as it is for any medical or other specialist to offer advice in individual health or family matters without being familiar even with the simplest facts of human genetics, or the apparently safe dosage-level effects of radiation.

Since specific counseling problems of clinical genetics require careful evaluation in terms of the total health and adjustment levels of a given family, it is understood that they are not to be dealt with in an *impersonal* way. To house the various functions of genetic counseling work, therefore, well-organized clinics should be established at every major medical center. By correspondence it is difficult to form an opinion regarding the predictable stability of the home a young woman will share with her future husband, after a psychotic episode, or into which a child with a calculable morbidity risk will be born. When confronted with potential health risks connected with marriage or parenthood, one of our main considerations ought to be that every child born in this age of growing concern for the welfare of children "should be given a fair chance in life" (25).

If these golden rules for the conduct and attitude of workers in human genetics carry a trace of rebellion against our dear mother science of basic genetics, let me propose to you that we remain rebels a while longer—preferably until we are certain that all the exacting

functions and objectives of our discipline have been fulfilled. As previously defined, the professional spirit should contain "elements of both conformity and nonconformity" (20). While it emphasizes adherence to the principles of scientific truth and ethical conduct, it also recognizes the rights and value of the rebel with a fresh viewpoint. Above all, the spirit of our discipline embodies the ideal of service and sacrifice—service to the people who need help, and detachment, in the words of Vannevar Bush, "from the mad scramble after this world's goods" (20).

We know the immense scope of the potential contributions of human genetics to the intelligent planning of man's health, welfare, and survival. Let us proceed to make them, either here or when we return to our work in the laboratory, the classroom, and the public health field.

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