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EDITORIAL

Of Privilege and Disadvantage

THESE ARE TIMES when it is often an advantage to be "disadvantaged," as when seeking an educational opportunity for example, or to belong to a "repressed" ethnic minority if one is seeking certain kinds of jobs. This is true in spite of the fact that laws which were passed in recent years to protect the rights of just these disadvantaged minorities would seem to prohibit precisely this kind of discrimination. One hears words such as "justice," "dignity," "equality," "rights," "demands," "power," "reparations" and sometimes even "destroy" being used by certain militant minority groups who seek what they consider to be parity (and, some observers suspect, an even larger role) in American society. One senses that a trend is developing where the extremes of the social and economic scale are to be the privileged while the great majority in between may be approaching underprivilege, and this in spite of the fact that it is they who do most of the work and pay most of the bills whether through taxes or otherwise.

In recent years the temper of the American people has been to eliminate both special privilege and special disadvantage as quickly as possible. Laws have been enacted and court decisions have been rendered to hasten the process. The thrust has been for greater freedom for individual expression and fulfillment on the one hand, and for equal opportunity and equal access for all on the other. It is tacitly assumed, though never actually spelled out, that fulfillment for an individual should never be at the expense of the same right for others, and that equality of opportunity does not necessarily mean equality of accomplishment or reward. It also is obviously not intended that minorities shall rule, whether by force or otherwise, nor is it expected or possible that minorities shall by fiat disappear, since almost everyone in America belongs to a minority of one sort or another. In fact American society itself is a unique amalgam of these minorities.

Since special privilege is no more a part of the American ideal than is repression, it is therefore paradoxical and perhaps in the long run unwise for the minorities considered disadvantaged to strive for equality by seeking or demanding special privilege, whether this be through persuasion or threat of force. Not only is this means to the end logically unacceptable, it also produces an instinctive adverse reaction among those who are in the majority, who have the vote and who pay the bills, and who more often than not belong to some racial or religious minority which at one time or another was also disadvantaged, repressed or perhaps even persecuted.

The situation that is developing needs more understanding, and this as soon as possible. If special privilege is to be reduced or eliminated, this will not be accomplished by encouraging or condoning special privilege. If the majority is to rule then a minority cannot call the tune. The evidence on both the state and national scene is that the reaction of the majority, though silent and unorganized, is beginning to make itself felt. If more serious difficulties are to be avoided it is imperative that a balance be quickly struck between privilege and disadvantage, whether this be in medical care, in education or in society itself. Only as soon as this

is accomplished to the satisfaction of the silent majority may it be expected that some very much needed funds for medical care, education and other equally important purposes will again begin to flow. These are times when reason, not bias, must prevail. Physicians have an important responsibility to influence the course of these events, both in medicine and in society.

Pharmacogenetics

IN PART GENETICS is concerned with the study of the causes of biologic variation. One of the major expressions of biologic variation lies in the reaction of an organism to changes in the environment. In man the use of drugs represents the introduction from exogenous sources of substances which change the internal or external environment of cells. It is not surprising that the remarkable genetic heterogeneity among individuals may be expressed now and again in differences in reactions to drugs. This is the topic of the Medical Staff Conference presented elsewhere in this issue. In a sense this topic is supplementary to that of drug interactions as a cause of unexpected action or inaction of pharmacological agents, a subject reviewed in detail in CALIFORNIA MEDICINE within the past year.[1]

The interaction of genetic and environmental influences may be difficult to disentangle in the individual phenotype, a classical problem which has roiled and embroiled almost all who have ventured into these murky waters. In quasi-despair, and with chromosome in cheek, it has been stated as a rule of thumb that if a kid looks like his father, it is genetic; if he looks like a neighbor, it is environmental. It is increasingly clear that the genetic legacy of the individual spells out in nucleotide sequences not only the imprint of normality and the misprints of specific genetic diseases, but also the messages which allow for metabolic adaptation and defense. These encoded messages may also go awry, often best illustrated by the altered response to drugs.

Pharmacogenetics, a relatively recent field of scientific inquiry, is usually considered in terms of the influence of genetics on drug action. It might equally be concerned with the influence of drugs on genetic action, perhaps even of greater importance when more fully elucidated. The genetic endowment of the individual, expressed phenotypically in protein structure, configuration, and concentration, may alter drug action or reaction in several ways:

(a) There may be an alteration in drug metabolism *per se*. This is usually reflected in the intensity and duration of its action rather than in some qualitative alteration in response. The amount of the active agent available to its receptor site is altered (increased or decreased) because of genetically determined variations in inactivation, transport, or excretion. Deficiency of pseudocholinesterase will decidedly prolong the action of the muscle relaxant suxamethonium. In the absence of the drug the enzyme defect appears to carry with it no biological disadvantage.

(b) Genetic variation may have a direct effect on drug action. It is presumed that this represents an alteration in the receptor site such that the response to the agent is depressed (or enhanced) with no variation in its metabolism. The best example of this category of pharmacogenetics lies in genetic resistance to the action of coumarin as described by O'Reilly and coworkers,[2] and cited as one example in the Medical Staff Conference. It is intriguing to speculate that studies of such genetic variants may clarify the normal mechanism of action of this group of anticoagulants, now far from clear. Some of the best examples of presumed genetic alterations in receptor sites are in endocrinology, perhaps admissible in this discussion by considering hormones as natural product drugs. Pseudohypoparathyroidism, vasopressin-resistant diabetes insipidus and testicular feminization represent diminished to absent responsiveness to hormones as diverse in structure and function as parathormone, vasopressin, and testosterone, respectively.

(c) The adverse reactions to drugs may be altered (usually enhanced, although this may represent bias in ascertainment) by genetically transmitted vulnerability. The mechanisms involved may be very indirect. Some excellent examples of this have been discussed in the Medical Staff Conference: hemolytic anemia secondary to glucose-6-phosphate dehydrogenase deficiency, hemolytic