GENETIC FACTORS IN RELATION TO DRUGS[1]

By W. Kalow
Department of Pharmacology, University of Toronto, Toronto 5, Canada

In pharmacology, individual variation in response to drugs is a broad field suitable for genetic studies. The study becomes most significant if variation is due to differences resulting from a single gene product, like an enzyme or other protein. The present review is, therefore, mostly concerned with this aspect of the topic, and because of limitations of space has been restricted almost exclusively to selected human data. The arbitrary nature of this choice is evident if one contemplates the recent splendid studies (33, 36, 37), conducted with the aid of drug-resistant bacteria, which indicate that streptomycin is able to cause false readings of the genetic code. For other pharmacogenetic observations on bacteria, single cells, insects, and mammals, the reader must be referred to a previous monograph (109) and a more recent one dealing only with mammals (149). A number of review articles have surveyed hereditary factors which determine human responsiveness to drugs (31, 54, 55, 56, 57, 108, 111, 113, 150, 153, 157, 193). Each of these review articles presents a selection of material which, in part, depends on the inclination of the author. In this respect, the present review is no exception, but some fresh examples and some new views have become available. A guiding principle in the selection of references has been to provide access to pertinent bibliography; recent papers have been selected for review—often at the cost of older key papers, particularly if the latter have been quoted previously (109).

Animals for Drug Research and Genetics

Every pharmacologist would like to be handed the ideal experimental animal for his research. Geneticists and breeders try to be obliging and, so, have produced a large variety of genetically-standardized animals. These animals may be random bred, inbred, or hybrid. They may not only be rats and mice; they may be beagles or miniature pigs. With all this variety at hand, nobody is able to predict which animal will be best for a given purpose. A group of inbred animals does not necessarily respond more uniformly to a drug than does a group of random-breds or hybrids; whether or not they do has to be decided empirically from case to case (80, 109, 149). The broad advantage of working with animals of known stock lies in the chance of increasing the reproducibility of one's experimental data, but there is no guarantee that this will always be realized.

Of unquestionable value is the availability of special-purpose animals, e.g., mice with muscular dystrophy, rats with a defect of glucuronidation, etc. (149). Also, there is much interesting literature on differences in the re-

[1] The survey of literature for this review was completed in July, 1964.

sponse to various drugs between strains or breeds of animals (109, 149). However, because of the multiplicity of differences between strains, there is not much chance of this kind of observation assuming great importance unless it is coupled with breeding procedures and detailed analyses. Models of what should be done are the studies on teratogenic activity of cortisone in mice (69, 116) and the recent work on the dextran-induced anaphylactoid reaction in rats (90, 91).

Succinylcholine and the Variants of Pseudocholinesterase

The characteristic brevity of action of succinylcholine in man is due to its rapid hydrolysis by pseudocholinesterase. The existence of hereditary variants of this enzyme explains many cases of prolonged effect of succinylcholine which are occasionally encountered during its clinical use. Several reviews of the subject (73, 85, 105, 109, 113, 130, 134) are available.

The first variant found, atypical esterase, most probably differs from the usual enzyme in amino acid composition since the two enzyme types can be separated by chromatography (73, 136), although their sialic acid content appears to be the same (185). Their reported (136) electrophoretic separation could not be confirmed (185). The structural deviation must affect, primarily, the anionic site in the active centre of the esterase. All esters of choline (38) or amines like procaine (68, 105) have a reduced apparent affinity for atypical cholinesterase. This is not true for the uncharged substrate α-naphthylacetate (7) and probably not for *o*-nitrophenylbutyrate, since the latter tends to be hydrolysed at the same average rates in sera with normal and atypical esterase (145). For inhibitors, the situation is somewhat more complicated. The inhibitory capacity of all quaternary and tertiary amines for atypical esterase is relatively low (106). Organic phosphates inhibit the two enzyme types to the same extent, although the rate of onset of inhibition is at least sometimes dissimilar; additional data are needed. Urea (115) and sodium chloride (89), in high concentrations, inhibit the hydrolysis of benzylcholine by atypical esterase more than that by the usual type. Anions have unpredictable effects as is evident from a comparison between chloride and fluoride (89) and between various types of buffer salts (105). Noteworthy is the resistance of atypical esterase to inhibition by fluoride (84) which has most peculiar inhibition characteristics in that it is an effective inhibitor of usual pseudocholinesterase only within an intermediate range of benzoylcholine concentrations (115).

Rubinstein, Dietz & Czebotar (168) reported, in a brief note, the occurrence of a lipid-soluble, fluorescent compound in the urine of persons homozygous for atypical esterase. This compound also appeared in the urine of persons with usual esterase, after treatment with the inhibitor pyridostigmine. Thus, the appearance of this compound may be indicative of a functional failure of pseudocholinesterase. One hopes that confirmation of the report and identification of the compound will lead to the discovery of the physiological function of the enzyme.

Methods of detecting atypical esterase (87, 102, 110, 167, 180) have been reviewed recently (113). Experiences with the diffusion test (87) have since been reported (74). A new hypotensive agent (tetralyl-allyl-alanin-diethyl-amide), which also proved to be a cholinesterase inhibitor, was reported to discriminate between serum cholinesterase of men and women (93). This report of sex discrimination is erroneous (115) and was apparently caused by the chance occurrence of a few heterozygous females in a small sample. The amide is an efficient tool for discrimination between usual and atypical esterase. The prevalence of atypical esterase (Table I) is similar in many populations (113) but may be slightly higher in Israel (186).

TABLE I

HEREDITARY VARIANTS OF PSEUDOCHOLINESTERASE RESULTING FROM FOUR ALLEIC GENES[a]

	Genotype[b]	Phenotype[b]	Prevalence[c]	Enzyme Status	Response to Succinylcholine	DN (102)	FN (84)
Homozygotes	$E_1^uE_1^u$	U	1:1	Usual type of esterase	Normal (103)	80	60
	$E_1^aE_1^a$	A	1:2500	Atypical esterase	Grossly prolonged (103)	20	20
	$E_1^sE_1^s$	S	1:100,000	No activity	Grossly prolonged (115)		
	$E_1^fE_1^f$	F	rare	Insufficiently investigated	Prolonged (132)	70	30
Heterozygotes	$E_1^uE_1^a$	I	1:25	Mixture of enzymes	Almost normal (103)	60	45
	$E_1^uE_1^f$	UF		Mixture of enzymes	Almost normal (115, 132)	75	50
	$E_1^aE_1^f$	IF		Mixture of enzymes	Prolonged (112, 132)	45	35
	$E_1^uE_1^s$	U	1:200	Usual type, decreased activity[d]	Almost normal (115)	80	60
	$E_1^aE_1^s$	A	1:8000	Atypical esterase, decreased activity[d]	Grossly prolonged (103, 109)	20	20
	$E_1^fE_1^s$	F		Not observed	(Prolonged)	[70]	[30]

[a] Cf. Tables in references (73, 109, 132, 134, 153).

[b] Discussions to avoid confusion of terminology were initiated at the Second International Meeting on Human Genetics, The Hague, September, 1963. The terms and symbols used here were drafted in a conference of interested investigators and have appeared in print (104, 153). The complete information will be published.

[c] Estimates based on data in references (107) and (175) and explained in reference (113).

[d] Persons genealogically identified as heterozygotes for the silent gene have, on the average, less enzyme activity than do the respective homozygotes (175).

Harris & Whittaker (84) described a set of observations which suggest the existence of another variant of pseudocholinesterase in man, a fluoride-resistant type. The sera were recognized as special because the esterase showed nearly-normal susceptibility to inhibition by dibucaine, while fluoride inhibition was reduced. Hence, in order to recognize the fluoride-resistant type, one has to compare the effects of two inhibitors with fluoride having most complicated enzyme kinetics. This renders the test open to many errors and accounts for the lack of data on the prevalence of this esterase variant in populations. In spite of these difficulties, some family data have become

available (138), and it has become clear that the presence of this variant affects the action of succinylcholine (112, 132). An improvement in the method of detection of the variant would be most desirable.

One person in perhaps 100,000 (175) has no pseudocholinesterase activity at all (43, 137). The reasons could be either absence or inactivity of the enzyme molecule. Hodgkin et al. (97) found no immunological evidence for the existence of an inactive enzyme protein; but, in view of the technical difficulties and of the shortness of the report, this may not be the last word. Genetic studies of the "silent gene" have been facilitated by its occasional occurrence in combination with atypical esterase (75, 105, 175).

The C^5 variant is recognized by electrophoresis (83, 86). It is so named because it looks somewhat like the fifth member of an isozymic series, while there are usually only four members in the system of Harris et al. (88) [cf., however, (12, 46, 134)]. Harris' fifth band is visible only on a slightly acid starch gel or after two-dimensional electrophoresis. Sera with the C^5 variant show, on the average, 30 percent more enzyme activity than do controls of the usual type (83). In regard to inhibition characteristics, C^5 does not differ from any of the other bands, and its presence does not seem to be particularly important for the interpretation of drug actions.

Harris et al. (86) found the C^5 variant in 5 percent of the British population. While the mode of inheritance has not been fully established, it is clear that C^5 is controlled by genes at a different locus from that for the four alleles which control the other known variants (Table I). Omitting the C^5 variant from further discussion, there are ten different genotypes. Due to the existence of the silent gene, the genotype cannot necessarily be recognized from the phenotype. For instance, a person whose cholinesterase in plasma is exclusively of the atypical variety may be homozygous for atypical esterase, or he may be heterozygous, carrying a silent gene together with one for atypical esterase. In spite of the control of esterase structure by genes, there is evidence for an environmental influence on the concentration of esterase (174). One may, therefore, speculate that esterase formation may be inducible in man, as it is in chicken embryos (23), and in *Pseudomonas*, (76), and as are other glycoproteins of human serum (29).

Although several local anaesthetics are hydrolysed at a reduced rate in sera with atypical esterase (68, 105), this does not ordinarily seem to cause clinical difficulties, perhaps because local anaesthetics are usually not given by intravenous injection. The prolongation of action of succinylcholine in the presence of atypical esterase has been thought to be caused by the low affinity which renders the enzyme so inefficient as to become inactive towards succinylcholine *in vivo* (104, 109, 112). It was, therefore, of interest to note that the duration of action of succinylcholine was approximately alike in persons without any pseudocholinesterase and in those with atypical esterase (115). In the latter, doses of 0.5 mg of succinylcholine per kg cause roughly an hour's apnoea instead of the usual one or two min (103). Vickers (192) reported recently that the apnoea may last for many hours, instead of the one

hour, if neostigmine is given too soon in a misguided effort to overcome a dual block; neostigmine may be of some benefit in cases of esterase failure after the succinylcholine-caused paralysis has lasted for an hour or more.

Lehmann & Liddell (133) have criticized Telfer, MacDonald & Dinwoodie (189) for reporting prolonged apnoea after succinylcholine in heterozygous persons who have a mixture of usual and atypical esterase. This criticism is justified both by the results of dose-response investigations (103) and by the fact that the prevalence of such heterozygotes is far greater than the proportion of succinylcholine-sensitive patients (133). On the other hand, there is no reason to doubt the observation of Telfer, MacDonald & Dinwoodie since it is not unique (68, 112). Even patients with normal type and level of esterase activity occasionally show prolonged effects of succinylcholine. Heterozygous patients or patients with any reduction of esterase activity are relatively often in the same category (109, 112). The reasons remain to be investigated.

Primaquine Sensitivity and the Deficiencies of Glucose-6-phosphate dehydrogenase (G-6-PD)

While the first observations on hemolysis following administration of aminoquinolins date back to the 1920's [cf. ref. (13)], it was not until 1954 that sensitivity to primaquine was proven to be attributable to an intrinsic abnormality of the erythrocyte and not to any abnormal extra-corpuscular factor (41). After one knew where to look, primaquine sensitivity was finally correlated with a shortage of glucose-6-phosphate dehydrogenase (G-6-PD), although one still does not fully understand why this renders the red cell liable to destruction. Since it has been recognized that there are various defects of G-6-PD (123) with a wide range of susceptibilities and of clinical expressions, the historical term "primaquine sensitivity" is frequently replaced by the designation "G-6-PD deficiency". While there are approximately 500 papers dealing with the deficiency and with closely related problems, two reviews may be singled out as reflecting, comprehensively and clearly, the knowledge accumulated to the dates of their appearance (13, 188). The present task is to present a summary and to indicate areas of recent progress.

The different forms of G-6-PD deficiency (123).—G-6-PD has been partially purified (6, 121). The enzyme requires the presence of triphosphopyridine nucleotide (TPN) for stability (122, 191).

A relatively mild form of G-6-PD deficiency occurs in American Negroes and affects 8 to 12 percent of the males. The concentration of G-6-PD in red cells is diminished to 8 to 15 percent of that in controls (124), but is normal (143) or variable (169) in leucocytes. The essence of the disorder is presumably an increased rate of destruction of the enzyme, since the activity of G-6-PD falls off distinctly in aging erythrocytes; a lack of stabilizing factors

in the erythrocyte may be responsible (144). There are, among Negroes, two variants of G-6-PD which differ slightly in electrophoretic mobility and which are not directly related to primaquine sensitivity. However, most sensitive individuals have the more mobile variant (125).

A relatively severe form of primaquine sensitivity is found in persons from southern Europe, the Near East, and Asia. G-6-PD activity is very low towards the normal substrate glucose-6-phosphate but surprisingly high towards 2 deoxyglucose-6-phosphate (127). The enzyme shows altered pH optima and is labile (127); its electrophoretic mobility is normal. What appears to be its concentration is diminished not only in erythrocytes but also in other cells (162, 163). The defect is most abundant among Sardinians and among some groups of Sephardic (Asiatic) Jews, in whom almost half the population is affected. Fava beans and several drugs in ordinary doses (e.g., aminosalicylic acid, chloramphenicol, quinine) have caused hemolysis in primaquine sensitive Mediterraneans but not in Negroes (188).

A defect characterized by very labile G-6-PD (126) is found in northern Europe. The red cells are so vulnerable that they tend to disintegrate spontaneously, and this condition is known as congenital nonspherocytic hemolytic anemia. Hemolysis has been accelerated by the presence of quinine (52). Very recently, it has been shown that congenital nonspherocytic hemolytic anemia is, biochemically, not uniform. There are at least two subtypes differing in kinetic behaviour of G-6-PD (126). In addition, the same kind of hemolytic anemia has been described as a consequence of deficiency of any one of four other enzymes, e.g., adenosinetriphosphatase (92). The precise characterisation of drug effects in these disorders will be interesting.

Genetics.—The genes (125) affecting G-6-PD are located on the X chromosome (30); therefore, all the deficiencies are sex-linked characters. This has, among others, the following consequences: primaquine sensitivity is never transferred from father to son and occurs more often among males than among females; while the males either are or are not sensitive, females may be heterozygous, i.e., they may have one normal gene and one causing enzyme deficiency. A peculiar thing in such females is that some of the red cells may be primaquine sensitive while others are not, the proportion being left to chance (15, 35); in other words, women may be genetic mosaics in respect to their red cells. Apparently the blood-forming organs develop early during embryonic life, before one of the X chromosomes is inactivated to become the Barr body.

Primaquine sensitivity is closely linked with deutan (green) colour blindness (161). The term linkage does not imply that two traits always tend to occur together, but that the loci for the two genes occur on the same chromosome close to each other. Hence, if a person happens to have both defects, his offspring is likely to have both; but in a large population, the two traits will as often be separate as go together. A tentative linkage map showing the loci for several traits on the X chromosome has been prepared (148); but, due

to chromosomal inversions, linkage data differ between populations (70, 176).

The variable prevalences of primaquine sensitivity in different populations has made one wonder what factors serve to preserve the mutation in some populations and not in others (120, 152). It now seems that primaquine-sensitive individuals have some resistance to falciparum malaria, so that the gene tends to accumulate in populations occupying malaria-infested areas (2, 67). On the other hand, damaging or fatal effects of hemolytic episodes must tend to eliminate the gene. Biologically, it is perhaps most important that deficiency of G-6-PD is sometimes strongly associated with neonatal jaundice and kernicterus (26, 63, 66, 158, 187). Primaquine sensitivity is, thus, an example of "balanced polymorphism".

Clinical tests.—For the detection of primaquine sensitivity, a number of tests are available. The well-tried glutathione stability test has been recently improved and simplified (16). Measurements of G-6-PD activity (50) may give a good discrimination in critical cases, since one is testing for the primary lesion. A G-6-PD spot test is available (60). For screening in the field, one may measure decolorisation time of brilliant cresyl blue (151), or one may use the methemoglobin reduction test (20, 21). A version of the latter test has also been worked out for precision measurements in the clinical laboratory (20, 21).

Drugs and hemolysis.—Large lists of drugs have been prepared to show the agents which have produced hemolysis of G-6-PD-deficient red cells (13, 109, 118, 188). In addition to a number of antimalarials, sulfonamides, nitrofurans, and antipyretics, the list includes dimercaprol (BAL), probenecid, water-soluble analogues of vitamin K, and chloramphenicol. Reports sent to the American Medical Association Registry on Adverse Reactions (17) show that in North America the drugs most frequently associated with hemolytic reactions of this type are naphthalene, nitrofurantoin, salicylazosulfapyridine (Azulfidine), sulfamethoxypyridazine (Kynex, Midicel), aminosalicylic acid (PAS), and sodium sulfoxone (Diasone sodium). This list reflects both the inherent ability to cause hemolysis and also rate of consumption in the United States.

The degree of hemolysis is dose dependent. Thus, hemolysis may be aggravated if drug levels persist in blood because of a failure of elimination. On the other hand, by careful choice of dose and an intermittent regimen, it is possible to mitigate the hemolytic effect of primaquine in sensitive persons and still retain therapeutic action (3).

The difficulties of elucidating the biochemical steps that lead to hemolysis are well illustrated by Carson's description (27) of sheep erythrocytes which behave like primaquine-sensitive human cells in all the pertinent biochemical tests, yet which are stable cells *in vivo* and *in vitro* and which do not hemolyse if primaquine is given to the sheep. Nevertheless, it must be important that reduced glutathione (GSH) disappears from human erythrocytes on drug

intake; GSH undoubtedly protects the hemoglobin sulfhydryls and the sulfhydryl-containing enzymes against oxidative destruction (27, 109, 188). The drugs causing hemolysis in these individuals have been called "oxidants" (51), although they are hydrogen donors. However, they are able to promote peroxidations in the presence of oxygen and water. Many of these drugs are known to be able to produce methemoglobin (14, 109); yet methemoglobinemia has never been a clinical problem in primaquine-sensitive individuals, probably because methemoglobin is preferentially formed in the old erythrocytes which tend to be absent in sensitive persons (22). The previously mentioned diagnostic test, the methemoglobin reduction test (20, 21), assesses the activity of G-6-PD *in vitro* by reduction of purposely produced methemoglobin.

Other Defects of Erythrocytes

In the presence of sickle-cell hemoglobin (HbS) (131), nitrous oxide, used with insufficient oxygen, has provoked sickling crises (32, 178). Besides anoxia, acidosis also favours sickling; and ammonium chloride, as used for acidifying therapy, is contra-indicated (139). Fever therapy has precipitated a crisis (129). While persons with sickle-cell disease are threatened most, there is some degree of danger to the heterozygous carriers with the sickle-cell trait (146) and to persons with sickle-cell hemoglobin C disease and with sickle-cell thalassaemia (101). Hemoglobin H is a tetramer consisting of four β chains (34). Inclusion bodies and hemolysis resulted from intake of sulfonamides by patients with hemoglobin H (164). A more serious hemolytic anaemia after the intake of sulfonamide has been shown to occur in persons with hemoglobin Zürich (71). While clinical reactions have been somewhat similar to those observed with hemoglobin H, the structural alteration (5) of hemoglobin Zürich involves the β chain and resembles the alteration encountered in one form of hemoglobin M, namely M_{Emory} (182); the latter is always present as methemoglobin. Motulsky (153) recently referred to unpublished data naming hemoglobin Seattle as another variant which is readily oxidized to methemoglobin by sulfisoxazole but which did not lead to hemolysis.

Methemoglobin formation is not only favoured in the presence of some abnormal hemoglobins, it may also be caused by an inherited defect in the production of an NAD-dependent methemoglobin reductase. Current knowledge in this field has been discussed in a recent paper by Cawein et al. (28). One must expect that persons with this defect are particularly endangered by cumulative effects of small doses of methemoglobin-forming agents (109).

Defects of Acetylation and the Metabolic Fate of Isoniazid and Other Drugs

It has been known for many years that there are rapid and slow inactivators of isoniazid (166); the methods for their determination have been reviewed recently (49). The inactivator status does not seem to make much

difference for antituberculous therapy, but it probably does for the occurrence of toxic drug reactions (57) if supplemental administration of pyridoxin is omitted (18, 42). Intestinal absorption, plasma binding, and renal clearance of isoniazid are the same in both rapid and slow inactivators (100), but the various metabolites of the drug are excreted in different proportions. Since the main metabolite of isoniazid in most people is acetyl-isoniazid [(1-isonicotinyl-2-acetyl hydrazine) (98)], there was reason to suspect that rapid and slow inactivators differed by their ability to acetylate the drug. This has now been proven in two independent investigations.

Evans & White (58) have correlated isoniazid metabolism of various persons *in vivo* with the ability of biopsy specimens of liver to metabolize the drug *in vitro*. Knowing the behaviour of biopsy specimens, the authors have extended their biochemical studies using autopsy specimens. They have, thereby, shown that the difference between rapid and slow inactivators of isoniazid lies in the activity of acetyl transferase. This enzyme transfers acetyl groups from acetyl coenzyme A to the drug molecule. The other line of evidence has been pursued by Peters, Miller & Brown (160) who administered not only isoniazid but also pure metabolites of isoniazid to various people and tested the patterns of urinary excretions. In this way, the defect could be shown to be solely one of acetylation.

The same acetyl transferase which acts upon isoniazid is apparently able to acetylate several other drugs (58). One of these is sulfamethazine which is acetylated by liver homogenates *in vitro* as is isoniazid. Sulfamethazine, if administered to people, can be used to classify individuals into slow and rapid acetylators. This observation should find much future use, since sulfa drugs are more easily measurable than is isoniazid. Two further drugs metabolized by this acetyl transferase in human liver are hydralazine (58) and phenelzine (Nardil) (59). Whether or not toxic side effects of these drugs occur predominantly in slow acetylators and how other MAO inhibitors are acetylated remain to be established.

Sulfanilamide (58) and *p*-aminobenzoic acid (58, 100) are readily acetylated, even by slow inactivators of isoniazid; there is no polymorphism in regard to their metabolism. Since liver homogenates were unable to acetylate these drugs, one must assume that their acetylation in the living organism takes place in some other organ.

Genetically, rapid acetylation is an autosomal dominant character (53, 128). This means that the presence of a single gene for acetylation enables a person to metabolize these drugs at a fairly rapid rate. The incidence of rapid inactivators varies greatly in different populations (184). In Caucasians and American Negroes, about half are rapid inactivators; among Eskimos, slow inactivators are almost absent. The incidence in various populations in Asia and, specifically, in Japan, has been investigated by Sunahara et al. (183, 184). A rapid acetylator in Asia is likely to metabolize the drug at a much faster rate than is a rapid acetylator in North America. Whether this indicates the existence of a series of major or of modifying genes remains to be seen.

Exceptional Resistance to Coumarin Anticoagulants

Link, who discovered bishydroxycoumarin (dicumarol), noticed large differences between rabbits in their susceptibility to its anticoagulant action (140). Since humans differ markedly in their ability to eliminate coumarin anticoagulants (198), Motulsky studied, systematically, this individual variation and obtained evidence for a normal distribution of the biological half-life of dicumarol in a human population. This suggests that multiple factors contribute to the individual variation, as one might expect since bishydroxycoumarin is metabolized by inducible enzymes (39). It is, therefore, especially noteworthy that O'Reilly et al. (159) observed a patient who did not appear to respond to an ordinary dose of Warfarin. Assuming that the average daily dose of Warfarin required to maintain a satisfactory state of anticoagulation is 7 mg and the standard deviation is 3 mg, the daily dose required by this patient was 145 mg and, thus, would be 46 standard deviations away from the mean. Also, this patient did not respond to bishydroxycoumarin and phenindione; he absorbed and metabolized Warfarin in a normal manner, and the protein-binding and volume of distribution of the drug were not different from those of controls. Dose-effect curves suggested that Warfarin had a low affinity for a receptor which was probably an enzyme concerned with the synthesis of the vitamin K-dependent clotting factors. Among nine members of the family of this patient, there were seven in three generations who were resistant to Warfarin, so that this trait appears to be controlled by a rare autosomal dominant gene.

Drugs and the Porphyrias

A serious problem in pharmacogenetics is the unmasking effect of barbiturates in "porphyria" which may lead to an attack of fatal paralysis (44). Unfortunately for the nonspecialist, porphyria may mean several different disorders of undefined relationship (165, 195, 197, 201). The danger of barbiturates is firmly established only in persons with acute intermittent porphyria and with the variegate porphyria (109). Waldenstrom & Haeger-Aronsen (195) now believe that many cases, formerly described as porphyria cutanea tarda, are, in fact, cases of this variegate porphyria. The latter has first been recognized among the Dutch settlers of South Africa, but the defect was introduced from Europe in 1688 (47). If one accepts this idea of Waldenstrom & Haeger-Aronsen, what remains under the name of porphyria cutanea tarda is a condition resulting from intoxication with the fungicide hexachlorobenzene (25, 170), the herbicide 2,4-dichlorophenol (19), and, last but not least, from chronic intake of alcohol. A hereditary predisposition to this disorder may exist (195) but is apparently no prerequisite. At the moment, the relevance of investigations of one form of porphyria for an understanding of another form is no longer obvious. Nevertheless, the studies by Granick on drug-induced porphyrias in animals deserve attention (77, 78), because they introduce a new idea into mammalian pharmacogenetics. The data imply that

"porphyria" may be a hereditary defect, characterized by failure of an enzyme repressor, and that drugs may induce formation of this enzyme because the repression is weak. The enzyme is δ-amino levulinic acid synthetase, the first enzyme in the synthetic chain concerned with porphyrin synthesis.

Mydriatics, Corticosteroids, and Glaucoma

Increased intraocular pressure is pathognomonic of glaucoma, although individual eyes vary greatly in their susceptibility to nerve damage by elevated pressure. Of the numerous kinds of glaucoma (135), the two most frequently occurring types are angle-closure and chronic, simple glaucoma. The predisposing factor for angle-closure glaucoma is a narrow angle of the interior chamber. This chamber angle is essentially under hereditary control (117. 190, 194). Attacks of angle-closure are brought about by pupillary dilatation which mechanically blocks the outflow of the aqueous into the canal of Schlemm. In eyes thus predisposed, mydriatic drugs, i.e., cholinergic blockers like atropine or adrenergic agents, may cause an attack of glaucoma (79, 109). It deserves emphasis that epinephrine usually decreases intraocular pressure (45), but may cause an increase in the presence of a narrow chamber angle.

A completely different type of glaucoma is chronic simple glaucoma, an insidious disease. The primary lesion is apparently an alteration of the trabecular mesh work, the spongy tissue through which the aqueous humor passes when leaving the eye (141, 179). One might postulate that some alteration involving protein (10) or mucopolysaccharide changes the permeability of this critical tissue. This glaucoma has long been known to have a hereditary basis (194). In a series of enlightening studies, Becker and his coworkers (8, 9, 11) have shown that topical application of dexamethasone and other corticosteroids decreases the outflow facility and causes a striking increase of intraocular pressure in patients with simple glaucoma and many of their relatives. A control population contained only very few individuals in whom corticosteroids had this effect, and these were probably candidates for glaucoma. While the biochemical mechanisms remain to be elucidated, this pharmacological test is of importance because it seems to detect the hereditary predisposition of potential victims of glaucoma. Early treatment can, thus, be instituted, and one may hope that this will save many persons from blindness.

Vitamins

Vitamin-D-resistant rickets has been reviewed previously in fair detail (109). Additional data have been published recently (24), essentially without change of original concepts. Some infants receiving a normal amount of vitamin D per day develop "idiopathic hypercalcemia" as a sign of vitamin-D intoxication (181). In some cases, the basis may be an inborn error of metabolism with defective inactivation of vitamin D (62, 119).

Pernicious anemia results from malabsorption of vitamin B_{12}, either because of a destruction of intrinsic factor by an immunological reaction (171),

or hereditary absence or dysfunction of this factor (147). Recently, another familial malabsorption syndrome of vitamin B_{12} has been described (99) in which intrinsic factor is present. The authors speculated that the so-called releasing factor (96), necessary for cobalamin absorption in the rat, may also be necessary in the human intestine and that this factor may be missing. Furthermore, it is becoming increasingly evident that not only macrocytic but also microcytic anemias can have a hereditary basis, which in the latter may be a defect of iron metabolism (173).

From the study of convulsive disorders related to pyridoxine deficiency (81), a special entity was separated and called pyridoxine dependency (142, 172, 196). Affected patients need continuous supplemental pyridoxine to maintain life. The essence may be a metabolic defect involving γ-aminobutyric acid. Gericke (72) performed studies on β-carotene, using twins and families, giving 4.5 mg per kg orally in oil. The measurements of vitamin A and of four other fractions suggest hereditary influence on absorption and rate of oxidation of the carotene.

Miscellaneous Observations

There is a rare hereditary condition called muscular subaortic stenosis (199), whereby the ventricular septum is a thick muscle which tends to obstruct the aortic valve. Incipient cardiac failure with ventricular dilatation tends to alleviate the obstruction and to increase the blood flow into the aorta. Under these conditions, some paradoxical drug effects may occur (200). Thus, decrease of cardiac size by digitalis may be fatal; and drugs that decrease peripheral resistance, e.g., amyl nitrite, may cause a transient rise in ventricular blood pressure.

Angst (4), in Switzerland, came to the conclusion that familial and, therefore, probably genetic factors determined the effects of imipramine. The conclusion is based on data from 61 families in which two or more members were treated for endogenous depression.

A relatively mild exposure to vanadium, which may occur as an occupational hazard and which is harmless to most people, may aggravate Wilson's disease (154). The cause of this disease is a hereditary deficiency of copper-transporting protein.

Acatalasemia (lack of catalase) was first discovered in Japan but is now known, also, in other countries (1, 82). Hydrogen peroxide, when applied therapeutically to mucous membranes, does not cause the usual foaming, and the tissue may turn black.

Hereditary alterations of reactions to anaesthetic drugs have been reviewed recently (108, 113). Perhaps the most striking report is that of Denborough et al. (40) who have described a white family in Australia in which general anaesthesia has been fatal in 10 of 38 members at risk. The sequence of events was hyperthermia, followed by convulsions, coma, and death.

The liver enzyme glucuronyl transferase is involved in drug metabolism and several hereditary diseases (111). If this enzyme is deficient, the glu-

curonidation of aminopyrine and of acetylsalicylic acid has been shown to be altered. There is a host of other hereditary disorders affecting the liver which may play a role in the hepatotoxicity of drugs (109, 111).

Of the various hereditary failures of odour perception, the widespread inability to smell hydrocyanic acid should be publicized, because this disability, when unrecognized, may lead to accidents in chemical laboratories (109). Important for the geneticists are the person-to-person differences in the ability to perceive the bitter taste of dilute solutions of phenylthiocarbamide (65). The ability to taste or not to taste is associated with various diseases (61, 94, 95, 177), but the biochemical mechanism is not understood. It is of some interest to note that nontasters of phenylthiocarbamide also have a reduced ability to taste thiopental or propylthiouracil, and some of them also fail to taste quinine (64).

Theoretical Aspects of Pharmacogenetics

Responsiveness to drugs is often normally distributed in a population. This is not so if a segment of the population is substantially different from the rest, as may happen for genetic reasons. In that case, distribution of responsiveness is usually bimodal; *vice versa*, finding a bimodal distribution may be the start of a genetic discovery. Murphy (155) has, therefore, critically assessed many errors that may lead one to overlook a bimodality or else to create one which is an artefact. Routine methods used in pharmacological assays to determine an ED_{50} can obscure bimodality almost by design (114). In order to increase the chance of finding hereditary parameters affecting drug metabolism, Nelson (156) has given some simple equations to sort out rate constants in studies concerned with the elimination of drugs. The potential use of population genetics to analyse the prevalence of uncommon intoxications has been described previously (109).

Recently, pharmacogenetics has been called "a new discipline" (48). Whether or not this is justified, work of pharmacologists and geneticists towards a common goal seems to result not in an additive effect but in a potentiation.

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