THE YEAR BOOK
of
DRUG THERAPY
1973

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EDITED BY

DALE G. FRIEND, M.S., M.D.

Associate Clinical Professor of Medicine, Harvard Medical School;
Head, Division of Clinical Pharmacology,
Peter Bent Brigham Hospital;
Member, Revision Committee, U.S. Pharmacopeia, 1960-1970;
Member, Pharmacy and Therapeutics Committees,
Peter Bent Brigham Hospital,
New England Baptist Hospital and the Veterans Administration

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The material covered in this volume represents literature reviewed up to October, 1972.

INTRODUCTION

Drug therapy continues to grow in importance. New technics that measure drug levels and drug actions are providing valuable information. For example, cardiac glycoside levels are now measured at many centers, and for the first time we are finding variations in the potency of these drugs. Efforts are being made to establish a single standard to which all cardiac glycosides must conform. In addition, nitroglycerin preparations have been found in many cases to be subpotent or even inactive. Because nitroglycerin is volatile, it is absorbed by plastic, cotton, cardboard and other packaging materials and thus its activity is reduced. These findings now cast doubt on much of the previous experimental work done with nitroglycerin. Studies that showed nitroglycerin to be no better than a placebo or only weakly effective may have been conducted with defective preparations.

Early enthusiasm for the use of the prostaglandins as an abortifacient and to induce labor has been tempered by further studies. Although prostaglandin therapy represents a real advance in obstetrics, their possibilities in other areas remain to be evaluated.

New drugs as well as new uses for existing drugs continue to hold our interest. A new agent effective against candidiasis has been studied. Levodopa has been useful in ameliorating the athetosis of cerebral palsy. A new derivative related to metronidazol has shown promise in the treatment of amebic dysentery. Propranolol seems to block the euphoria produced by heroin and may prove useful in treating the chronic addict.

Numerous articles are now appearing that deal with pharmacogenetics and drug interaction. These relatively new concepts are becoming increasingly important. The genetic constitution of the patient may profoundly influence his reaction to a drug. In some patients, drug interaction has been found to create unusual results. Many previously unexplained drug effects are now recognized as being due to these factors. The normal action of a drug may be so altered as to be useless, weak, superpotent or toxic or cause a serious untoward reaction.

Because of the importance of this subject, I am pleased to present a special article on pharmacogenetics, written by Gilbert S. Omenn and Arno G. Motulsky. The material will be included in a forthcoming book, *Human Behavior Genetics*, edited by A. P. Kaplan and published by Charles C Thomas. I hope you will find this excursion into basic pharmacologic material interesting and helpful.

D.G.F.

PHARMACOGENETICS

GILBERT S. OMENN and ARNO G. MOTULSKY

Department of Medicine (Division of Medical Genetics) and Genetics, University of Washington, Seattle

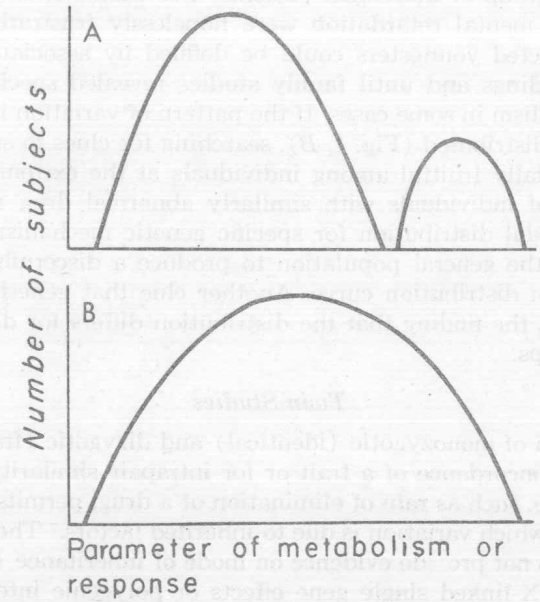
The term "pharmacogenetics" refers to studies of genetically determined individual differences in therapeutic and adverse responses to drugs.[1-3] These differences may be due to different rates of metabolism or elimination of the pharmacologically active species or may be due to different susceptibility to the drug action on specific enzymes or cell receptors. Recent reviews of such host-determined drug effects have emphasized their clinical and investigational importance as examples of gene-environment interaction.[4-6]

Methods of Analysis in Pharmacogenetics

Population Surveys

When a drug is tested in a general population sample or is used therapeutically in patients with any given diagnosis, considerable variability in effectiveness and in side effects is commonly noted. When drug potency, mode of administration and pertinent dietary factors are carefully stand-

Fig. 1.—Schematic diagram of discontinuous (*A*) and continuous (*B*) distributions of drug effects in population samples.



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ardized, three sources of variation still must be expected. First, some individuals will need a larger or a smaller dose than the average in order to attain the same effect or same plasma concentration of drug; some individuals may fail to show the desired effect at any reasonable dose. Second, some patients may fail to respond because the diagnosis is incorrect or because the diagnostic category comprises two or more distinct subpopulations, only one of which is responsive to the drug therapy provided. Third, especially when response is measured in subjective behavioral symptoms, attitudes of the patients and expectations of the volunteer subjects may be highly variable and influential: however, this source of variability often can be controlled with careful double-blind and crossover protocols for administration of the drug and an appropriate placebo. Figure 1 presents in schematic form the patterns of variation observed when human populations are tested.

Family Studies

If a bimodal distribution of response or side effects is suggested by the population survey, families of individual probands from all of the modal subpopulations should be tested. As in the case of acetylation of isoniazid, a simple inherited pattern may emerge from such family studies. At the least, family studies have the major advantage that the same mechanism for an unusual response to a drug or for a particular behavioral syndrome is more likely to be responsible in all affected members of one family than in a random group of individual patients. For example, investigations of the causes of mental retardation were hopelessly frustrating until subgroups of affected youngsters could be defined by associated clinical or laboratory findings and until family studies revealed specific inborn errors of metabolism in some cases. If the pattern of variation is more nearly continuously distributed (Fig. 1, *B*), searching for clues to subpopulations may be especially fruitful among individuals at the extremes. Studies of the families of individuals with similarly abnormal drug reactions may reveal a bimodal distribution for specific genetic mechanisms of too low frequency in the general population to produce a discernible "hump" in the population distribution curve. Another clue that genetic factors may be involved is the finding that the distribution differs for different ethnic or racial groups.

Twin Studies

Comparison of monozygotic (identical) and dizygotic (fraternal) twins for rates of concordance of a trait or for intrapair similarity in a quantifiable measure, such as rate of elimination of a drug, permits estimation of the extent to which variation is due to inherited factors.[7] The twin method, however, does not provide evidence on mode of inheritance (i.e., recessive, dominant or X-linked single gene effects or polygenic interaction). The contribution of environmental variables also can be assessed by changing the environment, as in chronic versus acute administration of a drug, retesting the same twin pairs or studying monozygotic twin pairs reared apart

and reared together.[8] In the last case, the extent to which the environments differ for the monozygotic twins reared apart must be estimated independently.

Biochemical Studies

The likelihood of defining specific genetic mechanisms increases as investigations reach closer to the enzyme or other protein products of genes. Thus, a mutation in the gene for plasma pseudocholinesterase or for red blood cell glucose-6-phosphate dehydrogenase is expressed directly by the altered properties of these enzymes, but only indirectly by the adverse response to certain drugs of the individual carrying such a mutation. When individuals differ in plasma concentration of a drug on a given dose, the rate of absorption can be tested by comparing oral and intravenous routes. If the difference in steady-state concentration or rate of elimination persists upon intravenous administration, renal clearance and plasma-protein binding must be considered. The qualitative pattern of metabolites may suggest the enzymatic conversion (hydroxylation, glucuronidation, acetylation, hydrolysis, etc.) responsible for inactivating or transforming the drug. If rates of conversion are altered, assay of the appropriate enzyme activity in blood cells or fibroblasts or liver biopsy may be possible. Electrophoretic and kinetic properties of the enzyme may be altered if a mutation in the structural gene for that enzyme is the basis for the differential drug response. Finally, difference in tissue responsiveness may be gene determined, by alteration in receptor molecules. Little has been learned yet of specific drug receptor molecules, but there is likely to be variation among individuals at this level of drug action, as well.

Pharmacogenetics of Specific Drugs

Succinylcholine (Suxamethonium)

Because of its rapid onset and short duration of action, this depolarizing muscle relaxant is used widely in premedication for anesthesia and for shock treatment (electroconvulsive therapy). However, suxamethonium will cause apnea for up to several hours in about 1 in 2,500 Caucasians genetically at risk for this possible catastrophe. These individuals have an abnormal plasma enzyme, pseudocholinesterase (PsChE), which fails to carry out the usually rapid inactivation of the drug. Measurement of plasma enzyme activity in the patients and their relatives indicated possible autosomal recessive basis.[9] However, clear differentiation of homozygous normal (usual form E^uE^u), of heterozygous carriers (E^uE^a) and of homozygotes from the abnormal or atypical gene (E^aE^a) became feasible with Kalow's method of testing per cent inhibition of PsChE activity with an enzyme inhibitor called dibucaine.[10] The normal enzyme is strikingly inhibited, whereas the atypical enzyme is only slightly inhibited. Screening individuals with dibucaine and fluoride as inhibitors and also with electrophoresis has revealed several additional rare variant forms of PsChE. Some of these variant PsChE also predispose to suxamethonium sensi-

tivity. On the other hand, another variant, PsCh Cynthiana[11] causes resistance to suxamethonium; this enzyme variant (on a per molecule basis) is three times as active as the usual PsChE.

In the clinical use of suxamethonium, the psychiatrist or anesthetist should inquire about personal or family history of sensitivity and should have equipment available for sustained artificial respiration. A simple screening test[12] for PsChE sensitivity is available. There is almost no need to test Negro or Oriental patients, since the frequency of the E^a gene is much lower in those populations.[6] Enzyme replacement therapy for this genetic defect has been accomplished by injection of purified pseudocholinesterase into patients with prolonged apnea.[13]

Acetylation in the Liver

When a standard dose of the antituberculosis drug isoniazid (INH) was administered to a group of individuals, the distribution histograms of blood levels of INH 6 hours later and of percentage of the administered INH excreted free and unacetylated in the urine were bimodal (see Evans[5]). Twin studies showed great similarity between monozygotic twins and considerable difference between dizygotic twins.[19] Family studies showed that slow inactivators of INH develop higher blood levels, excrete a higher proportion of free drug in the urine and have a trait recessive to rapid inactivation.[15] The responsible enzyme is a liver acetylase which inactivates INH and phenelzine (Nardil), as well as hydralazine (Apresoline), dapsone and other sulfa drugs. Rapid inactivators have no demonstrable impairment of antituberculosis effect on standard doses of INH. However, slow inactivators have a greatly enhanced risk of undesirable side effects, primarily peripheral neuropathy, which can be avoided by concomitant administration of the B vitamin pyridoxine. When patients with both epilepsy and tuberculosis are given INH plus diphenylhydantoin (Dilantin), an important drug-drug interaction may occur. Among the slow activators, INH concentrations reach levels that inhibit metabolism of Dilantin by hepatic microsomal oxidases, thus leading to accumulation of Dilantin to toxic concentrations, with ataxia, nystagmus, and drowsiness.[16] Similarly, toxic side effects of the antidepressant phenelzine[17] occurred only in subjects with the slow acetylator phenotype. It should be noted that about 50% of Caucasians, 50% of Negroes and only 10-15% of Orientals are slow acetylators.[4] Certain other drugs, such as para-aminosalicylic acid, are acetylated, but not by this particular polymorphic N-acetyltransferase. For other compounds, including serotonin, that can be acetylated, it is not yet clear whether the polymorphic acetylating system is responsible.

Oxidant Drugs and G-6-PD Deficiency

Glucose-6-phosphate dehydrogenase (G-6-PD) is the first enzyme of the energy-generating pentose-phosphate shunt pathway, which is essential to maintaining the integrity of the red blood cell. G-6-PD deficiency is sex-linked, affecting up to 35% of males in certain Negro and Mediterranean population groups. A long list of drugs with oxidizing properties can precipitate acute hemolytic anemia in these otherwise healthy but genetically

predisposed individuals by overwhelming the capacity of a deficient G-6-PD. In this case, the drug does not interact directly with the abnormal enzyme; the affected tissue is more susceptible to drug injury than normal.[18] The Mediterranean-type G-6-PD deficiency is more severe than the Negro type, hence additional drugs with less strong oxidant properties are a threat. These drugs include primaquine and other 8-aminoquinoline antimalarial agents, sulfas, nitrofuran derivatives, phenacetin, acetanilide, antipyrines, probenecid, para-aminosalicylic acid and aspirin.[5] Some of these individuals also cannot tolerate eating the broad bean *Vicia fava* or even inhaling its pollen. Interestingly enough, long before G-6-PD deficiency was known, the Pythagoreans were said to have surrendered to their enemy rather than flee through a field of fava beans. Also, in Greek mythology, a particular sect allowed women, but not men, to eat the fava beans,[19] consistent with the X-linked recessive inheritance of G-6-PD deficiency! Fava beans contain high concentrations of L-dopa; formation of a derivative of L-dopa (but not L-dopa itself) may trigger attacks of favism in the susceptible person.[20] As new drugs with oxidant properties are introduced, certain individuals can be expected to be at greater risk for such undesirable side effects.

Hydrocortisone and ACTH

These agents are used for patients with multiple sclerosis, polymyalgia rheumatica and many other conditions. Either topical or systemic corticosteroids may elevate the intraocular pressure sufficiently to induce open-angle glaucoma. Both the basal level pressure and the extent of elevation caused by the steroids are genetically determined.[21] Family studies suggest that a single gene locus may be responsible, though the biochemical basis for this susceptibility is unknown. Especially in older patients, it may be important to test routinely for glaucoma before starting corticosteroids.

Another relevant "side effect" among the many associated with corticosteroid therapy is the precipitation of "ACTH or steroid psychosis." Since only a small proportion of patients have this complication, it is likely that they are in some way more susceptible than others.

Tricyclic Antidepressants: Nortriptyline

Sjöqvist and his colleagues[22] have taken the clinical observations of Angst[23] of marked individual differences in the therapeutic effect of the tricyclic antidepressants as the basis for detailed pharmacokinetic studies of nortriptyline. Side effects of nortriptyline, corrected for those associated with placebo, were correlated with the steady-state plasma concentration of the drug and not with the dose administered.[24] Plasma concentrations in a group of 39 twin pairs varied over a 10-fold range, and the much smaller intrapair differences for monozygotic as opposed to dizygotic twins indicated a major role for genetic factors. Three patients with very high plasma levels served as probands for family studies. No bimodality of plasma level could be found in any of these studies, and analysis of the variances in relatives of the extreme proposita versus random subjects suggests that polygenic inheritance is involved.[15] This finding appears to rule out control of the rate of elimination of nortriptyline by a single enzymatic reaction.

Probably several biochemical reactions with genetic variability are involved; however, the exact number of genes and their biochemical roles are unknown. Nortriptyline is metabolized primarily by hydroxylation.

Animal Studies

It is often dangerous to assume that other species metabolize drugs by the same pathways as does man. The patterns of metabolites of amphetamines, for example, are quite different when man is compared with the dog or with rabbit and guinea pig.[26] Nevertheless, strain differences in the metabolism of specific drugs can provide useful models for study of the enzymatic steps involved and for correlation of metabolic degradation with "therapeutic" and adverse physiologic or behavioral effects.[27]

In general, strain differences in behavioral effects of drugs have been measured at the behavioral level without determination of blood levels, patterns of excretion or activities of enzymes involved in biotransformation. Fuller[28] tested four inbred strains of mice for the effects of chlorpromazine and chlordiazepoxide on active and passive avoidance. The complicated genotype-drug interactions observed were interpreted to reflect differences in both kinetic drive and fear-motivated responses in the different strains. The tricyclic antidepressant imipramine can reverse reserpine-induced hypothermia in rats. In comparison with three other strains, the Long-Evans rats were less reactive to the antireserpine activity of imipramine and had lower desipramine-imipramine ratios in the brains; their hepatic microsomal oxidases were less active against imipramine and other substrates in vitro.[29] In addition, however, the Long-Evans rats seem to be less sensitive to the desipramine formed. No breeding experiments were reported. The effects on exploratory behavior of the anticholinergic drug scopolamine and the anticholinesterase agent eserine were strikingly different in two mouse strains and in their F_1 hybrid.[30] The interpretation of these results in terms of cholinergic facilitation of exploratory tendencies is clearly speculative, though other studies do suggest differences in acetylcholine content, acetylcholinesterase activity and biogenic amine metabolism among mouse strains.[31] The most extensive animal study of drug effects, neurotransmitter metabolism and a specific inherited behavioral phenotype is that of audiogenic seizure susceptibility,[32, 33] which will be discussed later in the section on epilepsy. The fact that strains and genera of animals may differ genetically in their responsiveness to certain drugs must be recognized as a serious problem in interpreting mechanisms of drug-modified behaviors and, of course, in the practical testing of effects and toxicity of new drugs.

Simply Inherited Behavioral Disorders with Special Vulnerability to Drugs

The Porphyrias

These genetically heterogeneous metabolic disorders of hepatic heme biosynthesis are vertically transmitted through families as autosomal dominant traits. The clinical syndromes occur in episodes of colicky abdominal

pain with constipation (due to autonomic neuropathy) and variable central nervous system involvement, including flaccid paralysis, agitated and paranoid depression, and schizophrenic behavior.[34-36] Porphyria may have been the cause of the intermittent "madness" of King George III of England.[37] In the Swedish type, or intermittent acute porphyria, biochemical diagnosis during the acute attack is highly reliable. However, the increased urinary excretion of porphyrin precursors may not be present before puberty or between attacks. Increased production of Δ-aminolevulinic acid (ALA) and porphobilinogen is due to higher than normal activity of the rate-limiting enzyme, ALA-synthetase, in the liver. The mechanism of the increased activity is not yet clarified, though heme feedback[38] and possibly steroid reductase activity[39] appear to be involved. In the South African type, called porphyria variegata, there is continuous fecal hyperexcretion of proto- and coproporphyrins and photosensitive dermatitis.[35]

Several common drugs induce higher activity of the ALA synthetase and may precipitate attacks in any of these predisposed individuals. These drugs include barbiturates, certain sulfonamides, the antifungal agent griseofulvin and possibly general anesthetics, ethanol and chloroquine.[36] Often the diagnosis has not been suspected at the time of a drug-precipitated attack. Thus, a patient after abdominal surgery may complain of recurrent abdominal pain and develop bizarre behavior, with hallucinations and paranoid delusions and limb weakness. The significance of preoperative or postoperative medications, especially "routine sleeping pills," may be overlooked unless this specific diagnosis is considered. The porphyrias are most common in individuals of European ancestry and are extremely rare among Negroes.[36] It is noteworthy that the gene for the South African type of porphyria has been traced back to a Dutch immigrant in the 17th century, yet the "disease" has been recognized only in the past 30-40 years after introduction of phenobarbital and sulfonamides.[35]

Familial Dysautonomia (Riley-Day Syndrome)

This autosomal recessive inherited disorder causes protean manifestations of neurogenic origin. Infants have difficulty swallowing and lack of overflow tears, followed by slow achievement of developmental milestones and recurrent pneumonia. Periodic crises of vomiting, abdominal pain, fever, flushing and sweating and evidence of emotional lability dominate childhood. Sensitivity to pain is diminished, taste discrimination is defective (fungiform papillae are absent) and mortality risks of surgery are increased.[40, 41] Recent studies indicate a deficient release of the enzyme dopamine-β-hydroxylase from norepinephrine-containing nerve terminals into the plasma;[42] this enzyme converts dopamine to norepinephrine and is released together with the norepinephrine upon stimulation.

Infusion of norepinephrine into dysautonomic patients produced a very exaggerated hypertensive response without bradycardia. Conversely, the parasympathomimetic drug methacholine gave an excessive hypotensive response without increase in heart rate, plus abdominal cramps, sweating and overflow tears.[40] These youngsters lack the radiating pains and flare response to intradermal histamine, unless pretreated with methacholine.

Also, they compensate poorly for conditions of decreased oxygen saturation. The relationship of such autonomic nervous system imbalance to emotional lability is, of course, unclear. This disorder is found only among Ashkenazi Jews.[41]

Lesch-Nyhan Syndrome

This X-linked recessive condition of young boys is characterized clinically by choreoathetosis, spasticity, mental retardation and a bizarre, compulsive behavior with self-mutilation of lips, fingers and eyes.[43, 44] Biochemically, there is hyperuricemia and excessive production of uric acid, due to complete deficiency of an enzyme in purine metabolism, hypoxanthine-guanine phosphoribosyl transferase (HGPRT). Uric acid nephropathy leading to uremia and tophaceous gout may result. The HGPRT activity is normally highest in the brain, particularly in the basal ganglions, providing a correlation with the choreoathetosis. However, the basis for the behavioral disorder is altogether unknown. Since certain drugs are transformed by the same phosphoribosyl transferase, HGPRT deficiency has pharmacogenetic consequences. The antineoplastic agent 6-mercaptopurine must be converted to its ribonucleotide by HGPRT in order to be active in vivo. The immunosuppressive agent azothioprine (Imuran) is first converted to 6-mercaptopurine and then activated in the same manner. HGPRT-deficient fibroblasts in culture are resistant to inhibition by these drugs of *de novo* purine synthesis. Allopurinol is a valuable drug in the treatment of hyperuricemia and gout, since it blocks the conversion of hypoxanthine and xanthine to uric acid, which is less soluble and forms uric acid stones. Allopurinol normally also decreases purine synthesis, so that total xanthine excretion is less than that of uric acid. In HGPRT-deficient individuals, allopurinol ribonucleotide is not formed, so purine synthesis is not inhibited and xanthine oxidase is subjected to a higher concentration of active free base. As a result, these patients are liable to formation of xanthine stones. Partial deficiency of HGPRT has been recognized as a rare cause of "ordinary" gout, without the striking childhood neurologic and behavioral syndrome.

Malignant Hyperthermia

This condition has been recognized recently as an inherited predisposition to anesthetic catastrophes.[45] Potent inhalational anesthetics (such as halothane, methoxyflurane and ether) and muscle relaxants (such as succinylcholine) may trigger a rapid rise in body temperature and progressive muscular rigidity. Temperatures have reached 112 F., with tachycardia, tachypnea, hypoxia, respiratory and metabolic acidosis, hyperpotassemia, hypocalcemia and death from cardiac arrest in about two thirds of reported cases. The first of at least 14 familial cases was reported in 1962.[46] Apparently, individual fatal cases previously were just attributed to anoxic brain damage. The predisposition appears to be inherited as an autosomal dominant trait, with variable expressivity and incomplete penetrance,[47]

depending on exposure to anesthesia. The underlying basis is unknown, though patients who develop muscular rigidity often have had one of a variety of common musculoskeletal disorders.[37]

Kalow *et al.*[48] have studied muscle biopsies from survivors of malignant hyperpyrexia. Such muscle preparations were more sensitive to caffeine-induced rigor than muscle of normal controls; this effect was enhanced by exposure to halothane; and halothane depressed calcium uptake by the sarcoplasmic reticulum, whereas it had no such effect on that of normal controls. An important animal model for this syndrome has been discovered by halothane screening in Landrace pigs.[47] Intravenous procaine treatment, based upon the knowledge that procaine can block the effects on calcium binding by sarcoplasmic reticulum and the induction of muscle rigor by caffeine, was effective in preventing and treating this syndrome in a group of susceptible pigs.[50] No report of procaine therapy in human beings has yet appeared. Others have suggested that oxidative phosphorylation or cyclic AMP metabolism may be involved.[45, 51] There appears to be no relationship between suxamethonium-induced malignant hyperthermia and plasma pseudocholinesterase activity.

Huntington's Chorea

This autosomal dominant neurologic and psychiatric disorder is one of the major problems in counseling in medical genetics. The age of onset of involuntary movements is usually in the 30s or 40s, but may be delayed even longer. Thus individuals at risk (50% risk if a parent is affected) have the dual misery of not knowing whether they will be transmitting the disease to their children and of worrying that any "normal" twitches or behavioral problems may be the early signs of the disease. Over a period of 10-20 years, the affected person undergoes progressive deterioration of personality and of mental function, usually requiring institutional care because of psychotic behavior or dementia or both. The pathophysiology of the disease is unknown, and no specific diagnostic test is yet available. Two indirect diagnostic approaches have been considered. First, the genetic locus for Huntington's chorea might be closely linked to some other gene whose product is easily tested, like a blood group. It is now possible in suitable pedigrees to use linkage to the secretor locus to make an early diagnosis of myotonic dystrophy, another autosomal dominant disorder with late age of onset.[52] However, no such linkage relationship is known for Huntington's chorea. The second approach is a pharmacologic challenge. Since L-dopa administration to patients with parkinsonism may induce involuntary, choreiform movements, it was speculated that carriers of the gene for Huntington's chorea might manifest such movements at a lower dose of L-dopa than do normal people or parkinsonism patients.[53] There is a reasonable fear that the symptoms induced in the preclinical stage might not be reversible.[54] Certainly, individuals at risk will differ in their desire to know or to not know whether they will be affected later.

Pharmacogenetics in Specific Behavioral Disorders

Depression (Affective Disorders)

There is considerable evidence from twin and family studies that depression and especially manic-depressive psychosis is conditioned by genetic factors.[55, 56] A comprehensive pathophysiologic hypothesis involving biogenic amine metabolism has been formulated on the basis of multiple, but indirect, pharmacologic effects in patients with depression and mania. In brief, depression appears to be associated with decreased action or turnover of norepinephrine (and serotonin), whereas manic states are associated with increased biogenic amine turnover.[57] Thus, pharmacologic agents that deplete norepinephrine from nerve terminals (reserpine) or interfere with its biosynthesis (α-methyltyrosine, α-methyldopa) may precipitate depression. Drugs that enhance biosynthesis of norepinephrine (L-dopa) may induce hypomanic states, and agents that prolong the action of norepinephrine by inhibiting intraneuronal monoamine oxidase (MAO) inhibitors or the neuronal reuptake of norepinephrine released into the synapse (tricyclics) are effective antidepressants. Electroconvulsive shock also acts to increase tyrosine hydroxylase activity and norepinephrine turnover.[58] Two sets of clinical observations suggest likely pharmacogenetic relationships among patients with depression.

The first involves the differential effectiveness of antidepressant drugs in different patients. Pare *et al.*[59] reported that two groups of patients could be differentiated by their response to either MAO inhibitors or tricyclic compounds. In their hands, patients who responded to one class of antidepressant tended not to respond to the other. They asked two further questions. (1) Does the patient have the same pharmacologic responsiveness during a subsequent episode of depression, which might be precipitated by quite different life stresses? The answer was yes in 27 of 28 cases. (2) Do relatives of the patient who have an affective disorder share the same pattern of pharmacologic responsiveness and unresponsiveness? Again, the findings were positive, with 12 of 12 and 10 of 12 relatives concordant with the pattern of response in the proband patients in two separate studies.[59, 60] Angst[61] used only imipramine and found 34 relatives concordant with the proband for a positive antidepressant response, 4 concordant for lack of response and only 5 of 41 1st-degree relatives discordant. There is some skepticism about the distinctiveness of the treatment responsiveness in these studies. Pairs concordant for positive response might reflect, at least in part, the frequent favorable outcome with placebo administration in depressed patients.[62] Rarely were the relatives and probands both tested with both classes of drugs. The drug was not tested in unselected relatives, but only in those who were already identified as being affected with depression. Thus, the pattern of drug response and the predisposition to depression might be due to some common genetic mechanism, and the drug would serve to delineate two classes of depression, rather than just a difference in the metabolism of the particular drug. No biochemical studies to test this hypothesis have been carried out. It is

feasible to test the susceptibility of brain MAO to inhibition by typical MAO inhibitors, since patients who fail to respond might have a variant form of the enzyme that is not inhibited by usual concentrations of the drug. Such a situation would be analogous to the test of dibucaine inhibition of pseudocholinesterase in suxamethonium sensitivity.

The second clinical observation of pharmacogenetic interest is the risk that about 10% of patients treated for high blood pressure with reserpine will develop depression.[63, 64] These patients tend to have a personal history of affective disorder more often than do the 90% of reserpine-treated patients on whom depression does not develop.[64] Reserpine, in animals, is known to deplete neuronal stores of norepinephrine and serotonin and to induce an increase in activity of tyrosine hydroxylase, the rate-limiting step for biosynthesis of norepinephrine. It is conceivable that individuals differ in their capacity to step up norepinephrine biosynthesis or that individuals with low-normal stores of norepinephrine might be more severely depleted at similar doses of reserpine. Whatever the mechanism, it is likely that reserpine unmasks a predisposition to depression.

We have already noted that at least two types of antidepressant agents are subjected to genetic variation in their metabolism. Since phenelzine, an MAO inhibitor, is acetylated by the polymorphic hepatic acetylase system, individuals with the slow acetylator phenotype are more likely to experience side effects.[17] Likewise, standard doses of the tricyclic agent nortriptyline lead to variability in blood level and risk of side effects because of genetically determined differences in rate of metabolism.[24]

Finally, it should be emphasized that so general a phenotype as depression is likely to be predisposed to or mediated by multiple mechanisms, even if various alterations in biogenic amine metabolism serve as a common pathogenetic pathway. We should be alert to the possibility that differential responses to therapy and differential susceptibility to precipitation of attacks with reserpine or α-methyldopa or ACTH may provide insights and investigational "handles" into the heterogeneous causes of the syndrome.

Schizophrenia

Despite claims to the contrary, certain phenothiazines do not appear to be relatively better than others for different forms of schizophrenic illness.[65] Longitudinal follow-up of individual patients and family studies also fail to support clinical subtypes as a basis for sorting presumed heterogeneity in schizophrenia.[66]

Phenothiazines induce extrapyramidal side effects in an increasing proportion of patients as dosage is raised. The risk of parkinsonian symptoms from these agents is significantly higher in those patients with a positive family history of spontaneous Parkinson's disease.[67, 68] Presumably, the drugs unmask an inherited predisposition. Phenothiazines may also induce dramatic dystonic syndromes, including lockjaw, torticollis, and oculogyric crisis. It is not known whether the predisposition is the same as for the Parkinson syndrome. Furthermore, it is not known whether those patients

most susceptible to extrapyramidal side effects are also at greatest risk for cholestatic liver damage. If so, individual differences in blood levels might be the crucial variable.

Given the evidence for genetic predisposition to schizophrenia,[66, 69] it is reasonable to wonder whether individuals who have a schizophrenia-like reaction to amphetamines[70] are genetically predisposed to such psychotic reactions and would have been at relatively high risk for development of "spontaneous" schizophrenia. Pharmacologic deductions may provide insight into possible neurotransmitter mediation of at least some types of schizophrenia. The active groups of potent antipsychotic phenothiazines, when viewed in a three-dimensional molecular model, appear to resemble the molecular conformation of dopamine.[71] Amphetamines also act on biogenic amines, primarily through inhibition of the neuronal reuptake mechanism. In vitro studies of isolated synaptosomes from dopamine-rich and from norepinephrine-rich regions have shown that D-amphetamine and L-amphetamine are equipotent in the action on dopamine reuptake (dopamine lacks an optically active carbon), whereas D-amphetamine is ten times more potent than its L-steroisomer on norepinephrine reuptake (both amphetamine and norepinephrine have an asymmetric, optically active carbon). In vivo, a locomotor activity measure thought to be mediated by norepinephrine in rats is enhanced in a ratio of 10:1 by D- and L-amphetamine, whereas a stereotyped gnawing behavior thought to be mediated by dopamine is elicited at a 1:1 ratio.[72] Finally, D- and L-amphetamine appear to be equipotent in inducing amphetamine psychosis, many features of which resemble schizophrenic syndromes.[73] Extension of such studies of genotype-drug interactions may reveal clinical heterogeneity and biochemical mechanisms for schizophrenia and for other behavioral disorders.

Experimental psychologists have noted that magnitude of LSD and psilocybin effects on perception is related to the variability that the particular subject showed on the perceptual or behavioral test before ingesting the drug.[74] Genetic factors in the biologic substrate may be involved in the lability or variability of such specific behaviors. It is not known, of course, whether such genetic factors might be the same as those predisposing to schizophrenia.

Seizure Disorders

The normal pattern of electric activity in the brain, as measured by the electroencephalogram (EEG), is determined almost entirely by genetic factors in a polygenic system, according to Voge.[75] In addition, several single-gene-mediated "variants" of the normal EEG have been described, affecting altogether about 15% of the general population (Table 1). The clinical significance of these variants is unknown. No studies have yet been carried out with groups of individuals having different baseline EEG patterns to see whether there are different responses to various psychopharmacologic agents. The EEG variation provides an intermediate level of evidence between the observable variation in human behavior and the biochemical variation at the level of individual enzymes in brain tissue of different people. One older study of phenobarbital effects found induction