Today's Treatment

Clinical pharmacology

Possible clinical importance of genetic differences in drug metabolism

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How often we have heard conversations such as: "When I took that cold medication, I became very sleepy. But when my sister took the same dosage, she wasn't sleepy at all." Or "How can cigarettes cause lung cancer? Although my uncle (who smoked half a pack a day for 30 years) died of lung cancer at age 45, why doesn't my 80-year-old grandfather (who has been smoking two packs a day for more than 60 years) have lung cancer?" *Pharmacogenetics* research is the attempt to understand the hereditary basis for two individuals (with the possible exception of identical twins) responding differently to drugs or other foreign chemicals. These responses include not only therapeutic effects—for example, control of seizures—but also undesirable effects such as increased risk of drug toxicity or cancer.

Genetic differences in drug metabolic pathways

In any pharmacology textbook most drugs and other foreign chemicals are shown to be metabolised by numerous, sometimes competing, pathways (fig 1). Often there are more than a dozen possible intermediates and products. Because there is such a complicated network of interacting pathways, you might assume that pharmacogenetic differences typically would be expressed as *polygenic* (two or more genes) *multifactorial* traits, such as height, weight, intelligence quotient, or blood pressure. This assumption turns out often *not* to be true.

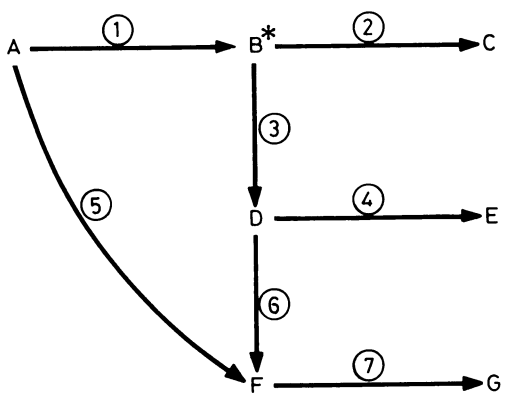

FIG 1—Schematic representation of cascading pathways by which most xenobiotics are metabolised.[1] A, parent drug; B* through G, various metabolites; *circled numbers* depict enzymes. [Reproduced with permission from Academic Press.]

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Why not? If, for example, in fig 1 compound A causes toxicity, any diminution of enzymes one or five would increase the steady-state concentration of compound A, thereby enhancing its duration and toxicity. If compound A requires metabolism to carcinogenic intermediate B*, any lowering of enzyme two, three, or five or enhancement of enzyme one would increase the steady-state concentration of the reactive intermediate, thereby causing greater risk of cancer. Moreover, if any of the other more distant enzymes such as four, six, or seven were rate-limiting for the overall pathway, any change in such an enzyme could be most important in affecting the steady-state concentration of compound A or B*. If the enzyme responsible for the rate-limiting step can vary by a large amount (twofold, but especially 10- or 100-fold) differences in the gene encoding that enzyme would predominate over any subtle changes ($\pm 50\%$) in the remainder of the enzymes concerned.

Phase I and phase II drug-metabolising enzymes

Most drugs and other environmental pollutants are so fat-soluble that they would remain in the body indefinitely were it not for the metabolism resulting in more water-soluble derivatives. These enzyme systems, located principally in the liver (but also present to some degree in virtually all tissues of the body), are usually divided into two groups: phases I and II. During phase I metabolism, one or more water-soluble groups (such as hydroxyl) are introduced into the fat-soluble parent molecule, thus allowing a "handle," or a position, for the phase II conjugating enzymes to attack. Many phase I products, but especially the conjugated phase II products, are sufficiently water-soluble so that these chemicals are excreted readily from the body.[2]

Pharmacogenetic differences that may be clinically important

The table lists most of the human pharmacogenetic differences that have been described during the past 30 years. I have tried to be inclusive and apologise if any disorder has been inadvertently overlooked. In each instance a foreign chemical (hydrogen peroxide, drug, synthetic hormone, or other environmental pollutant) has been presented to a clinical population, and variable responses occur—due to underlying genetic differences in the uptake, binding, or fate of that chemical.

In this list are several examples of relatively simple (auto-

TABLE—*Arbitrary classification of human pharmacogenetic differences**

- Disorders with increased sensitivity to drugs (decreased detoxication due to less enzyme)
  - Acatalasia (acatalasaemia)
  - Pulmonary emphysema, liver diseases, associated with the Z allele of α_1-antitrypsin
  - Succinylcholine apnea
  - Bishydroxycoumarin sensitivity
  - Isoniazid or sulfamethazine "slow acetylator"
    - Peripheral neuropathy induced by isoniazid
    - Lupoid hepatitis induced by hydralazine, procainamide, phenelzine
    - (?) Idiopathic systemic lupus erythematosus
  - Crigler-Najjar syndrome
  - Phenytoin (diphenylhydantoin) toxicity
  - Debrisoquine 4-hydroxylase deficiency
- Differences resulting from increased resistance to drugs
  - Possibility of (or proved) defective receptor
    - Inability to taste phenylthiourea or phenylthiocarbamide
    - Coumarin resistance
    - Androgen resistance
    - Diabetes mellitus
    - Leprechaunism (insulin receptor)
    - Familial hypercholesterolaemia (LDL receptor)
    - Cystic fibrosis ([?] α-adrenergic, β-adrenergic, and cholinergic receptors)
  - Accelerated degradation rate of receptor
    - Myasthenia gravis
    - (?)Allergic rhinitis and asthma
  - Defective absorption
    - Juvenile pernicious anaemia
  - Increased metabolism
    - Succinylcholine resistance
    - Atypical liver alcohol dehydrogenases
    - Pentazocine resistance
  - Abnormal cell membrane function
    - Manic-depressive illness induced by decreased lithium transport
    - Primary hypertension caused by decreased sodium ion extrusion
- Disorders exacerbated by enzyme-inducing drugs
  - Hepatic porphyrias
  - Pentosuria
  - (?)Environmental carcinogenesis
    - Combustion products
    - Drugs that cause cancer
    - Other environmental pollutants
- Diseases in which toxification may play a part
  - Increased susceptibility to drug-induced haemolysis
    - Glucose-6-phosphate dehydrogenase deficiency
    - Other defects in glutathione formation or use
    - Haemoglobinopathies
  - Hereditary methemoglobinaemia
    - NADH-methaemoglobin reductase deficiency
    - Haemoglobinopathies
    - Paracetamol O-deethylase deficiency
  - Isoniazid-induced hepatitis in rapid acetylators
  - (?)Chloramphenicol-induced aplastic anaemia
  - (?)Halothane-induced liver necrosis
  - Vitamin D-dependent rickets
  - Hypoxanthine-guanine phosphoribosyltransferase (HGPRT)-deficient gout
  - Malignancy and drug toxicity associated with the human [*Ah*] complex
  - Drug-induced lipidosis characterised by a foam-cell syndrome resembling Niemann-Pick's disease
  - Scleroderma-like illness induced by *L*-5-hydroxytryptophan and carbidopa
- Disorders of unknown aetiology
  - Glaucoma induced by corticosteroid ophthalmic agents
  - Malignant hyperthermia caused by anaesthetics (halothane, succinylcholine, methoxyfluorane, ether, and cyclopropane)
  - Norepinephrine sensitivity and absence of flare in response to intradermal histamine in patients with familial dysautonomia (Riley-Day syndrome)
  - Phenytoin-induced protein synthesis and collagen production enhanced in cultured fibroblasts of patients with gingival hyperplasia caused by phenytoin
  - Thromboembolic complications caused by anovulatory agents
  - Atropine sensitivity in patients with Down's syndrome
  - Meperidine-induced jaundice
  - Norethisterone-induced jaundice
- Disorders associated with diet
  - Lactase polymorphisms
  - Fava bean-induced haemolytic anaemia
  - Coeliac disease
  - Familial hypercholesterolaemia
- Reported polymorphisms; clinical disorders not yet demonstrated
  - Enzymes in catecholamine metabolic pathway
    - Dopamine β-hydroxylase
    - Catechol O-methyltransferase
    - Monoamine oxidase
  - Leukocyte cytidine deaminase
  - Serum paraoxonase
  - Steroid hydroxylase deficiencies
  - Sulfite oxidase deficiency
  - Amobarbital N-hydroxylase deficiency
  - Phenytoin metabolism
  - Diphenhydramine metabolism
  - Antipyrine metabolism

*If the reader is interested in specific references concerning any of these disorders consult the text or *ref* 1, or address inquiries directly to the author.

somal dominant or recessive) genetic expression of drug-metabolising capability leading to striking differences in drug sensitivity or resistance, even among siblings. For example, Kutt[3] described three families in which certain members exhibited more than a threefold decrease in the normal metabolism (hydroxylation) of phenytoin, thereby resulting in toxicity when the patient received what was believed to be a "normal" dose. Idle and Smith[4] have found that deficiency in 4-hydroxydebrisoquine formation is expressed as an autosomal recessive trait; more than a 20-fold difference in this metabolism may occur between two members of the same family. O'Reilly[5] described in two large pedigrees the presence of an autosomal dominant trait for coumarin resistance; the required dose of anticoagulant for one patient may be five to 20 times larger than that for his sibling. Complete deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT) is responsible for the Lesch-Nyhan syndrome, an X-linked inborn error of metabolism characterised by neurological abnormalities, mental retardation, and compulsive self-mutilation.[6] Certain male patients with gout are hemizygotes, that is, the X-linked allele is defective—and the patients exhibit about 1% of the normal HGPRT activity. Hence, this genetic defect can reflect a 100-fold or more difference among family members in the metabolism of, for example, 6-mercaptopurine or allopurinol.

What is "cytochrome P-450?"

Most phase I oxidations are performed by cytochrome P-450. "Cytochrome," derived from Greek, literally means "coloured substance in the cell." The colour is derived from the subatomic properties of the iron in this haemoprotein, and, indeed, cytochromes appear reddish when sufficient concentrations exist in the test-tube.

"P-450" denotes a reddish pigment with the unusual property of having its major optical absorption peak (Soret maximum) at about 450 nm, when the material has been reduced and combined with carbon monoxide.[7] Although the name P-450 was intended to be temporary until more knowledge about this substance was known, the terminology has persisted for 17 years because of the increasing complexity of this enzyme system with each passing year and because of the lack of agreement on any better nomenclature.

What is metabolised by P-450?

Cytochrome P-450 clearly represents a family of isozymes possessing catalytic activity toward thousands of substrates. This collection of enzymes is known to metabolise: almost all drugs and laboratory reagents; small chemicals such as benzene, thiocyanate, or ethanol; polycyclic aromatic hydrocarbons such as benzo(a)pyrene (ubiquitous in city smog, cigarette smoke, and charcoal-cooked foods) and biphenyl; halogenated hydrocarbons such as polychlorinated and polybrominated biphenyls, defoliants, insecticides, and ingredients in soaps and deodorants; certain fungal toxins and antibiotics; many of the chemotherapeutic agents used to treat human cancer; strong mutagens such as N-methyl-N′-nitro-N-nitrosoguanidine and nitrosamines; aminoazo dyes and diazo compounds; various chemicals found in cosmetics and perfumes; numerous aromatic amines, such as those found in hair dyes, nitroaromatics, and heterocyclics; N-acetylarylamines and nitrofurans; wood terpenes; epoxides; carbamates; alkyl halides; safrole derivatives; antioxidants, other food additives, and many ingredients of foodstuffs, alcoholic beverages, and spices; both endogenous and synthetic steroids; prostaglandins; and other endogenous compounds such as biogenic amines, indoles, thyroxine, and fatty acids.

Detoxication versus toxification

Twenty or 30 years ago, it was believed that virtually all drugs and other environmental chemicals were pharmacologically active (or toxic, carcinogenic, mutagenic) in their parent (non-metabolised) form. The function of all drug-metabolising enzymes was therefore regarded as *detoxication*—that is, to "inactivate" the parent drug. More recently it has become evident that although some chemicals are, indeed, active in their non-metabolised form, most chemicals are inactive until they are being metabolised[2 8]; this process is

called *toxification*. Detoxication and toxification enzymes coexist in the same cell, in some instances architecturally next to one another in the same membrane. Numerous examples of proved or suspected detoxication or toxification—playing a part in human pharmacogenetic differences—are compiled in the table.

Having more of a particular enzyme cannot be predictably good or bad. For example, succinylcholine apnea is characterised by a low pseudocholinesterase activity,[9] so that the normal clinical dosage may be fatal. Patients with succinylcholine resistance exhibit cholinesterase activities about three times normal,[10] so that the normal dosage is relatively ineffective. Isoniazid may cause a toxic peripheral neuropathy in "slow acetylator" patients,[11] whereas isoniazid can produce fatal hepatitis in "rapid acetylator" patients.[12]

Some enzymes are responsible for detoxication of one drug and toxification of another. For example, low concentrations of a particular P-450 presumably account for debrisoquine 4-hydroxylase deficiency,[4] so that normal dosages of this drug will cause an appreciable orthostatic hypotensive effect. On the other hand, high concentrations of a particular P-450 presumably play a part in the risk of certain environmentally caused cancers, such as bronchial carcinoma [see ref 13 for review]. Human liver alcohol dehydrogenase metabolises digitoxigenin and related derivatives; cardiac activity of these digitalis-related drugs may be decreased by over 90%.[14] Genetic differences, or ethanol-induced differences, in alcohol dehydrogenase therefore may alter the required loading and maintenance doses of digitalis due to this potentially important detoxication pathway. Liver alcohol dehydrogenase also may toxify chemicals, because the enzyme metabolises several xylyl alcohols to aldehydes that are very toxic to lung tissue[15] and metabolises allyl alcohol to the extremely neurotoxic acrolein.[16]

Interplay between environmental factors and pharmacogenetics

A myriad of other factors also may contribute to the underlying genetic differences in drug metabolism.[17] These factors include changes in enzyme activity as a function of development and age, tissue distribution and specificity, enzyme inducibility, drug-drug interactions, various diseases, and hormonal and dietary state.

The phenomenon of "in-vitro activation" occurs in human as well as laboratory animal tissues, and genetic differences occur in man.[18,19] The possible clinical importance of these interesting data, however, remains unknown.

How many forms of P-450 are there?

Any form of P-450 believed to be highly purified still exhibits a large degree of overlapping substrate specificity. Thus, although one chemical may appear to be the best substrate, ten other drugs can easily be shown to be metabolised one-tenth as efficiently and another ten drugs can be shown to be metabolised one-hundredth as efficiently as the best substrate.[20,21] Until recently the general consensus among most laboratories has been that three, or six, or perhaps 10 or 20, forms of P-450 exist and that overlapping substrate specificity accounts for all the diversity seen when thousands of different chemicals are metabolised. At the other extreme, it has been postulated[22] that organisms have the genetic capacity to produce as many distinct forms as there are inducers of P-450. Possessing the genetic capacity to synthesise hundreds or thousands of different forms of P-450 does not imply that all of them would exist at any one time. In this respect the P-450 system might exist for the hundreds of thousands of environmental chemicals, as the immune system exists for the roughly one million antigens on this planet.

In terms of evolution and survival it might be reassuring to think that, if a new chemical is dumped into our water supply, our bodies have the capacity to recognise this new substance and mobilise the appropriate enzymes for detoxication. We have begun to test this interesting, yet provocative hypothesis[22] with the use of recombinant DNA technology.[23,24]

Demonstration of the complicatedness of multiple forms of P-450 by laboratory animal studies

Data from inbred strains of laboratory animals, in fact, probably helped to lull all of us into the naive thinking of the 1960s that the P-450 system was simple and straightforward. An example of this is illustrated in figure 2. These two particular

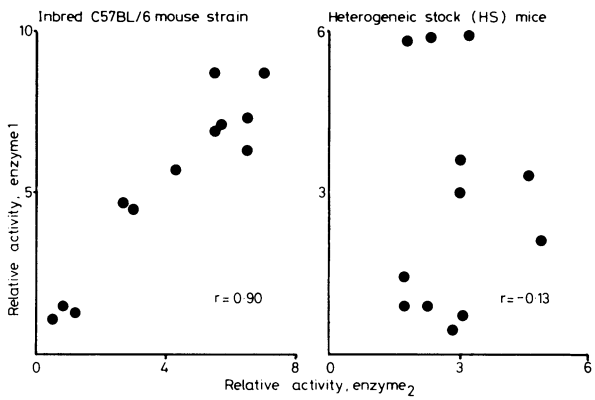

FIG 2—Experimental attempts to correlate two liver drug-metabolising enzyme activities among 12 inbred mice (*left*) and 12 heterogeneic (HS) mice (*right*). Both types of mice were divided into four groups of three each; relative enzyme activities were determined 0, 12, 24, and 48 h after intraperitoneal treatment with 3-methylcholanthrene, an inducer of certain forms of P-450. The two enzyme activities—believed to represent the same form of P-450 until about six years ago—are aryl hydrocarbon (benzo [a]pyrene) hydroxylase and 2-acetylaminofluorene N-hydroxylase, respectively.

drug-metabolising enzyme activities were chosen for illustration here because of the popular tenet that they represent the same form of P-450, most commonly referred to in pharmacology publications as "3-methylcholanthrene-induced cytochrome P-448." As it turns out, neither activity is "most closely associated" with P-448.[25,26] For example, if one examines 12 inbred mice (fig 2, left) the correlation coefficient between the two enzyme activities is excellent ($r=0{\cdot}90$). Compared with wild mice or randombred strains of mice, any particular strain of inbred laboratory animal is very homogeneous. In fact, colonies of wild mice are not believed to be as diverse as mice of heterogeneic stock (HS).*

HS mice are at least as heterogeneous as any outbred or randombred laboratory animal and, in fact, might approach the degree of variability found in man. With 12 HS mice (fig 2, right), the two enzyme activities clearly are not correlated ($r=-0{\cdot}13$). We have similarly studied over 20 drug-metabolising enzyme activities[25,26] and find that practically no activity correlates well with any other activity. Although such a study cannot determine the exact number of P-450s, we can conclude

*HS mice originated from an eight-way cross-population developed at the University of California at Berkeley by Dr Gerald E McClearn in collaboration with Dr W Meredith. The eight original strains[27] included: C57BL, A, C3H/2, BALB/c, DBA/2, AKR, RIII, and Is/Bi; all were sublines at the Berkeley Cancer Research Genetic Laboratory at the time. The mice were later imported to the Institute of Behavioral Genetics, University of Colorado at Boulder, where they are being maintained as a base stock with 40 mated pairs in each generation. Mates are assigned randomly with the restriction that mates cannot have a common grandparent. With such a large sample of matings used in each generation, this arrangement will maximise outbreeding and prevent many genes from segregation even after 10 or 20 years.

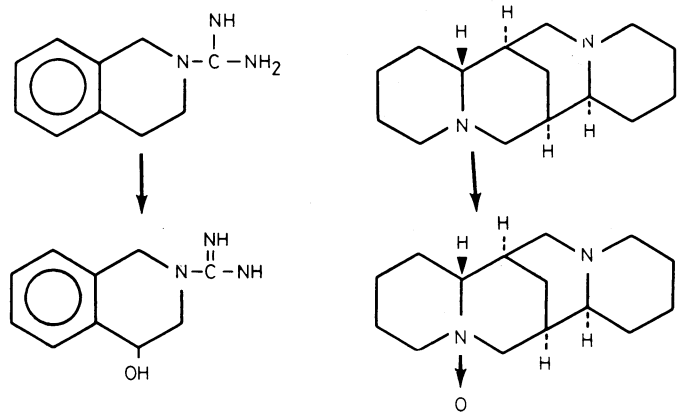

FIG 3—Metabolic pathways of debrisoquine 4-hydroxylation (*left*) and sparteine N-oxidation (*right*).

that almost every "drug-metabolising enzyme activity" appears to be unique and represents the contribution from multiple forms of P-450.

Is predictability in clinical pharmacology hopelessly complicated?

Ten to 15 years ago, clinical pharmacologists had hoped to "categorise" all drugs into three, five, or ten classes—one corresponding perhaps to "each form of P-450." If a patient were to receive an anaesthetic from "class A," for example, it was hoped that clinical pharmacologists could give some "class A test compound" and determine whether the patient was a slow or rapid metaboliser and therefore how much "class A anaesthesia" would be required. After dozens of such clinical studies, however, the conclusion today has become quite clear. Each patient appears to be genetically quite unique,

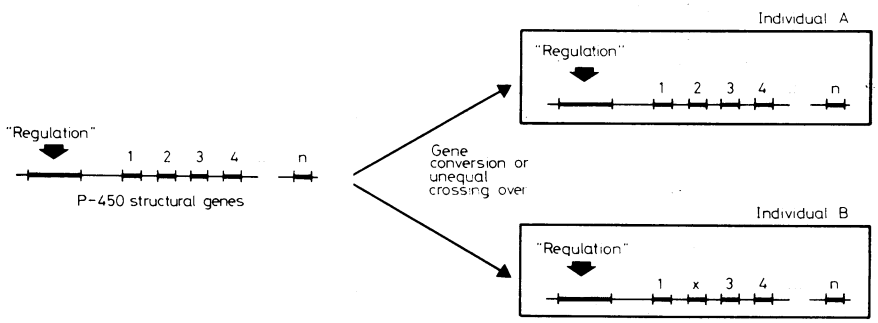

FIG 4—Heuristic diagram of P-450 structural genes as a closely linked multigene family. Number of structural genes for P-450 is currently unknown. Possibility of groups of P-450 structural genes on two or more chromosomes is also certainly tenable. Phenomena of gene conversion and unequal crossing-over[29] are two mechanisms by which there may have evolved individuals having a genetic difference in one of the structural genes of the multigene family (shown here as the replacement of P-450 gene number two with an "x").

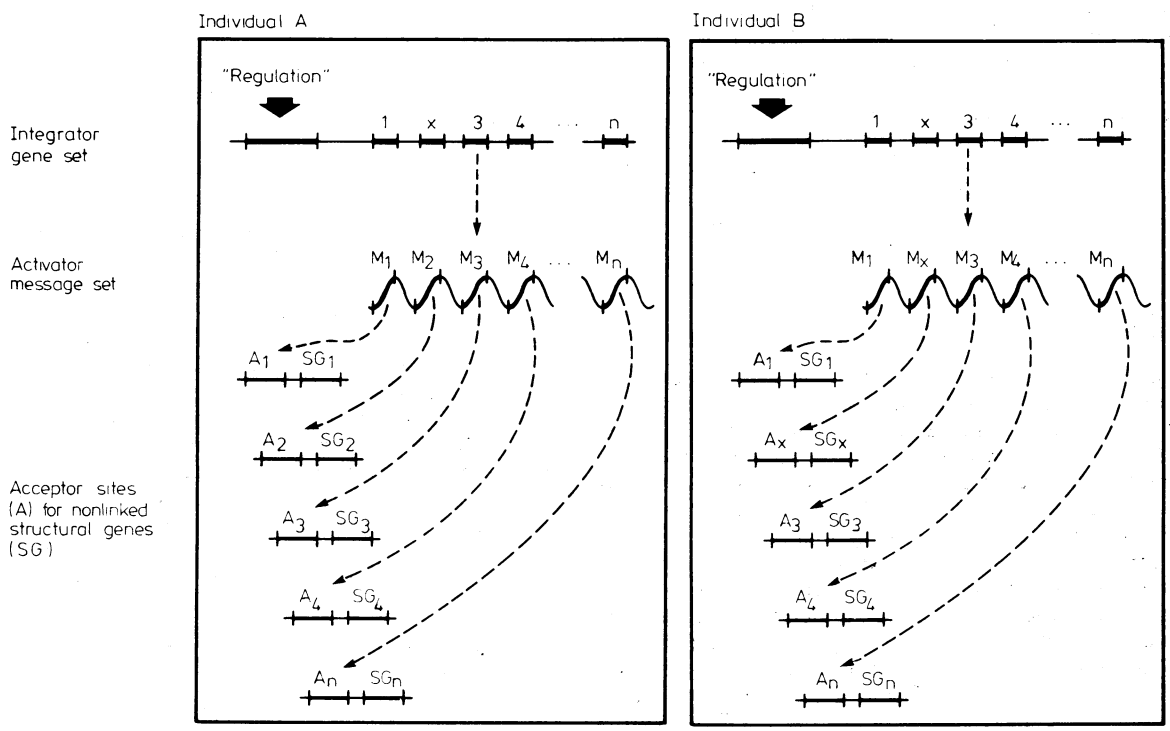

FIG 5—Heuristic diagram of P-450 structural genes (SG) not necessarily present on same chromosome. This hypothesis invokes the Britten-Davidson model[30] of an integrator gene set, transcription of these genes into activator mRNA (M) in nucleus, and activation of structural genes by binding of activator mRNA's to acceptor sites (A) adjacent to corresponding structural gene. This diffusion of genetic information (activator messages) to other chromosomes is also called *trans* genetic regulation. Again, as in fig 4, genetic difference is shown as replacement of P-450 gene number two with an "x". Hence, although gene conversion or unequal crossing-over occurs in integrator gene set, actual P-450 structural genes could be non-linked—that is, could be located on other end of same chromosome or on different chromosomes.

and our knowledge of the rate of metabolism of one drug cannot predict the rate of metabolism of practically any other drug. Drug response has become extremely empirical and anecdotal from one patient to the next.

Idle *et al*[4 28] have described a polymorphism of drug metabolism in human populations. If a patient has the autosomal recessive trait for debrisoquine 4-hydroxylase deficiency he is also deficient (to varying degrees) in the O-dealkylation of paracetamol and 4-methoxyamphetamine, the N-oxidation of sparteine, the aromatic hydroxylation of guanoxan and phenytoin, and the S-oxidation of metiamide. Most likely the genetic defect resides in one (or several) form(s) of constitutive P-450—that is, control forms specifically necessary for the biosynthesis or degradation of normal body substrates, such as steroids, fatty acids, or biogenic amines. In addition to its natural substrate, the form(s) of constitutive P-450 can accommodate to some degree these foreign substrates—that is, overlapping substrate specificity. In all likelihood new forms of P-450 could be induced, which would metabolise each of these drugs more efficiently than the form(s) of constitutive P-450. This hypothesis, not likely to be testable in man, could be proved or disproved in the laboratory animal.

A clinical experiment has recently been completed, however, and the data support very well my hypothesis stated above. R Idle *et al* (personal communication) studied 218 patients for both the 4-hydroxylation of debrisoquine and the N-oxidation of sparteine (fig 3). A total of 212 patients showed linkage for the metabolism of the two drugs—that is, the patients were either "rapid metabolisers" for both drugs or "slow metabolisers" for both drugs. Six patients, however, were "recombinants"—that is, the patients were either rapid metabolisers for debrisoquine and slow metabolisers for sparteine or vice versa. This finding, called *linkage disequilibrium*, therefore occurred with a frequency of about 3% among the British population examined. Hence, these data are evidence for P-450 structural genes that are closely linked yet distinctly different. Possible models for linkage disequilibrium are illustrated for linked P-450 structural genes (fig 4) and for non-linked P-450 structural genes (fig 5). I believe the hypothesis illustrated in fig 4 is the more likely, but the hypothesis illustrated in fig 5 cannot be ruled out at present.

Vesell and coworkers, with the use of identical and fraternal twins, recently have studied 4-hydroxyantipyrine, N-demethylantipyrine, and 3-hydroxymethylantipyrine formation. Each of the three metabolites appears to be caused by different form(s) of P-450 under separate, distinct genetic control.[31] The data from our laboratory[25 26] and the data described in this brief review therefore suggest that each of us may be as unique about our drug-metabolising capabilities as we are about having unique fingerprints. Patient A may rapidly metabolise debrisoquine and coumarin but slowly metabolise phenylbutazone and antipyrine; patient B may rapidly metabolise coumarin and antipyrine but slowly metabolise debrisoquine and phenylbutazone; patient C may be a slow metaboliser for all four of these drugs; patient D may form high amounts of 4-hydroxyantipyrine and N-demethylantipyrine but form small amounts of 3-hydroxymethylantipyrine; and so on. In other words, the chances for finding a "prototype drug" to test a person for his capacity as a rapid or slow metaboliser of any large or small "class" of drugs are probably nil.

Finally, what are the take-home messages to the practising doctor? (1) Whereas there may exist an "estimated normal dose" for a given drug, such a dose administered to any particular patient may be ineffective, or may be toxic—depending on the pharmacogenetic makeup of that patient. This result may occur with *any* drug, whether the patient is being treated for a bacterial infection or seizure disorder, or is receiving chemotherapy for cancer. (2) More and more assays for blood, saliva, or urine concentrations of drugs or metabolites are being developed each year. As these assays become less expensive, less time-consuming, and more popular, doctors will be able to monitor much more successfully the *effective* drug dosage for each individual patient. (3) At all times, however, the doctor should be aware that drug idiosyncrasies will occasionally occur and that there may be twofold, 20-fold, or even 100-fold differences in drug response, even among members of the same family. He must remember that, just as his patient has genetically determined colour of hair and eyes and unique fingerprints, he probably also has a unique genetically determined drug-metabolising capability.

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MATERIA NON MEDICA

Max Reger

Not very long ago Elgar and Vaughan Williams were regarded as non-contributors to the British GNP—too "English" and not very exportable. Fortunately, over the past decade they have both had a worldwide reappraisal, and with the help of the new generation of jet-set British conductors, their music has gained a new recognition abroad. It may come as a surprise to know that the Germans, the purveyors of staple musical diet to the world, have a similar difficulty with some of their own twentieth century heroes.

Max Reger (1873-1916), for example, has acquired a quite unjustified reputation as a first-division bore, a latter-day JS Bach look-and-sound-alike. This late Romantic, who worked at the same time that Arnold Schoenberg was shocking middle European sensibilities with his "new" music, placed a staggering number of notes on the scores of his 130-plus numbered works, written over a creative lifetime of only about 25 years. It is therefore no surprise that he did not produce 130 masterpieces. But some of them are masterpieces, and apart from a handful of choral and organ works they have been almost totally neglected.

Towards the end of his short life he wrote five monumental sets of variations on themes by Bach (his idol), Telemann, Mozart, Beethoven, and Hiller. The Bach set, for solo piano, will unfortunately never see the light of day in its original form (it was revived in the 1940s in a shortened form, arranged for two pianos): there are simply too many notes for a mere two-handed mortal to cope with; but his Telemann variations, obviously modelled on the Handel variations by Brahms, are much more approachable, but rarely performed. The Beethoven set, for two pianos, which (like the others) concludes with a fugue of dazzling complexity, has suffered the musicologists' kiss of death and would require intensive resuscitation and rehabilitation before taking its rightful place in the concert repertoire. The neglect of the two orchestral sets (on themes of Mozart and Hiller) is almost complete in Britain. This is a great loss, for they show the usually dour Reger at his most genial, as would befit a composer who replied to his critic on receipt of yet another brickbat (this time for his sinfonietta): "I am sitting in the smallest room of the house; I have your review in front of me. In a few seconds it will be behind me."—DAVID LEVY (SHO in gastroenterology, London NW10).

Toheroa soup

The rising sun was reflected from the virgin snow on the summits of the rugged Fiordland mountains. But we were still in daybreak shadows as we drove down the gravel road to Te Wae Wae Bay, at the extreme south of New Zealand's South Island. Gone was the wooden sign "Toheroa Season Closed." In its place were two weather-tanned rangers directing the little queue of cars on to the flat expanse of beach. For this was the long-awaited opening day of the toheroa season, the first that had been allowed for three years. The toheroa is New Zealand's, perhaps the world's, rarest delicacy, the bivalve shellfish which forms the main constituent of that gourmet's delight, toheroa soup. Known to and prized by the Maoris long before the European invasion, the shellfish was culled nearly to extinction; now found on only three New Zealand beaches it is rigorously protected outside the one-week season.

An amazing sight met our eyes as we rounded the headland. Almost as far as the eye could see the beach along the sea's edge was covered with groups of people feverishly digging in the cold wet sand with their bare hands. We parked our car with the scores of others and walked to join them with our bucket. A toheroa's presence is signalled by two small dimples in the sand. We spotted a pair immediately and laboriously scraped a hole: no digging implements were allowed. Suddenly, a good foot below the surface, we saw the creamy-grey shell. With difficulty, because its large extruded "foot" kept a surprisingly powerful grip, we pulled the toheroa free and cast about for the next dimples. Within 30 minutes we had collected our quota of 10 apiece, and thankfully we retired to the car to thaw out our cold numb hands on cups of steaming coffee.

Later in the morning we prised open the shells, extracted the inedible breathing tubes, and cut up the flesh, to stew it with milk, onions, and butter. The soup's flavour was elusive; we disagreed with the enthusiasts who liken it to oysters fed on a diet of asparagus tips. But what did we care? Not only was it one of the world's rarest dishes but it had been a gift of bountiful Nature.—GARTH HILL (Berkhamsted, Herts).

The fourth day

The following short story was written by Dominic Joyce for a story competition at his school. He wrote it a few days before his 11th birthday and three months after the death of his father's closest friend.

It was the fourth day.

Dead on the fifth day, the doctors had said. Nothing they could do. Go away, be alone. Eat little, sleep a lot. Conserve your energy, survive as long as you can.

And he had.

He wasn't hungry; but he ate, He wasn't sleepy; but he slept.

He was dying, but he didn't mind

In a way.

One thing, he thought in his waking hours, was that he dreamt. He hadn't dreamt since he was a young child.

He visited places he'd never seen and met people he'd never known. He himself was surprised he could dream such things. Perhaps it was the things he might have seen, the people he might have met. Always it had the same end. He dreamt he heard music. With it ran words. It went: Death is a dream, but dying is a nightmare. Dying is the terror of anticipation, but death is the falling of the blow. Dying without death, and death without caring.

It was his funeral march he said as the stone was laid into place. Yellow fingers of lichen reached up and covered the stone and the flowers curled and died.

Dying without death, he thought. I am dying but I am not dead.

Perhaps I will live, after burying my hopes. He flexed his fingers, looking at the way they moved, at the clever way he moved them, and at the way they fitted together so perfectly.

He remembered the things they could do that he had done with them, that he could, had done without thinking, caring, without knowing. He thought of his eyes and ears, all the time sending message after message to the brain. He wondered what kept his heart beating, what would happen when his eyes and ears stopped telling the brain what they saw and heard, when the hands stopped moving, the heart finally faltered and stopped, and what would happen to his mind when they did.

Then he thought of the song in his dream. "If dying is knowing you're going to die, then dying without death must be knowing you're going to die, about to die and not dying," he concluded. Satisfied with this, he lay down in the deep, dreamless sleep of healing.

The next day he dressed in new, clean clothes, and went out into the world, with nothing but a heavy breakfast, to see places he had never seen before, and meet people he had never met. It was a dream come true. It was the fifth day.—DOMINIC JOYCE (Bristol).