Pharmacogenetics and Anesthesia

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Pharmacogenetics deals with hereditary modifications of the response to drugs. The word pharmacogenetics is of recent origin but already has been used by several authors to head reviews and monographs. Interest in the subject has been initiated by the special medical and legal problems that arise when a hereditary defect causes a patient to be harmed by a conventional application of a conventional drug. On the other hand, observations in pharmacogenetics are a challenge and may become points of departure for diverse investigations. The potential scope of pharmacogenetics is wide since all forms of life exhibit genetic variation and are able to respond to drugs or chemicals. The following review, however, is confined to drugs used in man for or during anesthesia.

Of particular concern are hereditary characteristics which alter pharmacologic responsiveness but which are hidden and unrecognized prior to drug administration. Obvious hereditary diseases which may also cause abnormal pharmacologic responses pose different problems. Nevertheless, there are transitions since individual patients suffering from, say, porphyria, may come to the anesthetist with or without diagnosis. Included in the following discussion are, therefore, some comments on genes with ordinarily concealed effects and those with usually visible effects. However, there will be some bias in emphasis; relatively much space will be devoted to a description of the cholinesterase variants because of the author's special familiarity with this topic.

The Cholinesterase Variants

Many cases of "prolonged apnea" after succinylcholine can be explained by the existence of an atypical form of pseudocholinesterase.

The topic has been reviewed several times but the present survey is justified by a number of new observations. Furthermore, the occurrence of atypical esterase is still an occasional cause of anesthetic death.

At present, there are four genes recognized which control human pseudocholinesterase, not counting the gene which determines the usual esterase type. A few introductory paragraphs will therefore deal with biochemistry and means of determination of the esterase variants, to be followed by an outline of genetic aspects and a discussion of the clinical significance.

Classification of Esterase Types: Biological Characteristics and Means of Determination

Atypical Esterase. (1) Nature: Liddel et al. have described a means of physical separation of usual and atypical esterase by chromatography on a DEAE column. The ability to separate the two esterase types indicates that they are structurally different. Since the two enzyme types seem to contain the same amount of sialic acid, the difference is most likely in the content of amino acid.

As judged from the Michaelis constants, atypical esterase has a relatively low affinity for all investigated substrates. In addition, indirect evidence suggests that atypical esterase has mostly lower turnover rates than does the usual enzyme. These two functional defects render atypical esterase a very inefficient enzyme. The affinity of atypical esterase for succinylcholine is about 100 fold lower than that of usual esterase which appears to be

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Dr. Kalow has also reported a separation of esterase types by paper electrophoresis. In spite of considerable effort, the electrophoretic separation on paper could not be reproduced. There is certainly no electrophoretic separation on starch gel at any pH unless a small amount of decamethonium is incorporated into the gel.
TABLE 1. Genotypes in Regard to Pseudocholinesterase, Drawn Under the Assumption that the Four Genes are Alleles

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Probability</th>
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<tbody>
<tr>
<td>$E^aE^a$</td>
<td>$E^aE^a$</td>
</tr>
<tr>
<td>$E^aE^b$</td>
<td>$E^bE^b$</td>
</tr>
<tr>
<td>$E^aE^c$</td>
<td>$E^cE^c$</td>
</tr>
<tr>
<td>$E^dE^d$</td>
<td>$E^dE^d$</td>
</tr>
</tbody>
</table>

See text for reservations to this assumption. Underlining indicates susceptibility of the phenotypes to sucinylcholine.

$E^a$ = gene for usual esterase; $E^b$ = gene for atypical esterase; $E^c$ = gene for fluoride type; $E^d$ = silent gene.

the main reason for the failure of some patients to metabolize this drug.11 For procaine, both affinity and turnover rates are moderately decreased but this double decrease may cause the hydrolysis of procaine to be very slow.19

The relative affinity of atypical esterase for numerous inhibitors is even lower than that for substrates so that atypical esterase tends to be less inhibited than is the usual enzyme.22 Recently found exceptions are chloride23 and urea20 which, in high concentrations, inhibit atypical esterase slightly more than they block the usual esterase.

(2) Methods of Determination: Several methods of distinguishing atypical from usual esterase have been published. The first method24 utilizes the fact that atypical esterase shows diminished inhibition by the local anesthetic dibucaine (nupercaine, chinchocaine, percaine), using benzoylcholine as the substrate. Percentage inhibition observed under standard conditions is called Dibucaine Number (DN). Esterase activity is determined by ultraviolet spectrophotometry which requires relatively expensive equipment but permits one to keep track of the substrate itself and not only of a secondary function like pH. Also, the biochemical test system is very simple. The measurements are therefore inherently accurate. The method is fast enough to permit determination of esterase type while a patient is aneic in the operating room.

Steinicz et al.26 have determined DN using a colorimeter. Esterase activity is assessed by following changes of pH with the aid of color changes of an indicator.

Rubinstein and Deitz26 have recently described a method which is based on a comparison of the hydrolysis velocities of acetylcholine and benzoylcholine. The hydrolyses are measured either in a titrimeter or in a colorimeter.

For screening of samples in the spectrophotometer, a method has been devised17 which utilizes the neostigmine derivative R02-0683 instead of dibucaine. With this method, 50 sera have been classified routinely per two hours.

Harris and Robson27 have described two tests for screening large numbers of sera. The preferred test requires agar plates in which there are small circular wells for sera. Esterase activity determines the diameter of a stained circular field around the well. Staining is produced by a histochemical method using alpha-naphthylacetate as a substrate. Sera with atypical esterase can be spotted by adding R02-0683 or dibucaine to the agar. The agar plates require overnight incubation.

Since the kinetics of atypical esterase differ coarsely and in many ways from that of usual esterase,4 any of the cited methods would enable one to recognize persons homozygous (see below) for atypical esterase, and numerous additional methods could be devised. Problems of discrimination exist, and the choice of method may be important, if one wishes to recognize the heterozygotes who have a mixture of usual and atypical esterase, particularly if it happens that the normal esterase predominates in this mixture. The ability to recognize such a heterozygote is not vital for many diagnostic purposes but it is essential for family studies and is a prerequisite for most other work on esterase types.

Cholinesterase Anenzyma. There is a gene which causes lack of pseudocholinesterase activity.11 Lehman et al.28 called this a silent gene when they found a complete lack of esterase activity in a woman and a reduced esterase activity in her offspring and in her mother.

(1) Nature of the Deficiency: Lack of esterase activity is apparently not caused by enzyme inhibition. Thus, the lack could be either due to absence of the esterase protein or due to an alteration of the enzyme protein which renders it inactive. Hodgkin and associates29 have searched in vain by immuno-
logical for an inactive enzyme protein, but details have not been published.

(2) Methods of Determination: Persons with complete lack of esterase activity are easily recognized but are very rare. Otherwise, only family studies can reveal the silent gene. When testing DN in relatives of persons with atypical esterase, the silent gene shows up by the pattern of inheritance of atypical esterase.11,20

The "Fluoride Type." (1) Nature: The name "fluoride type" refers to a cholinesterase variant discovered by Harris and Whittaker with the aid of sodium fluoride as enzyme inhibitor.31,32

By starch gel electrophoresis at various pH, with and without prior removal of sialic acid from the esterase, the fluoride type is indistinguishable from both usual and atypical esterase.17 The variant represents presumably an enzyme alteration.33 Detailed kinetic data do not exist, but the affinity of the fluoride type for succinylcholine is at least somewhat reduced.20 This statement is based on in vitro tests and is consistent with observations on patients who have received succinylcholine.34,35

(2) Methods of Determination: The determination is based on the fact that the cholinesterase activity of some sera is relatively resistant to inhibition by sodium fluoride. The inhibition test is performed with sodium fluoride instead of dibucaine. In analogy to DN, per cent inhibition by fluoride under standard conditions is termed FN for Fluoride Number.31,32 At present, the determination of FN is the only means of identifying the variant. Unfortunately, the test is unsatisfactory for several reasons. First, atypical esterase is more resistant to fluoride inhibition than is the fluoride type itself. This increases the chances of error since any interpretation of FN must take into account the DN. Second, there is a peculiar dependence of FN on benzoylcholine concentration (to be published) so that FN, unlike DN, is influenced by any error affecting the substrate. Further uncontrolled variables seem to affect FN but addition of chelating agents did not help in stabilizing the action of fluoride.29

The Electrophoretically Identified C2 Variant. (1) Nature: After two-dimensional electrophoresis, Harris and co-workers36,37 have found a variant which shows up as a spot of esterase activity which is not present in all sera. In the test system employed, every serum shows at least four spots with esterase activity designed as C1 to C4, with most of the activity being in C1.31,35 Distinguishable from these is spot C2, which appears in some sera and represents an additional pseudocholinesterase. Sera with this additional enzyme hydrolyze benzoylcholine about 30 per cent faster on the average than does usual serum. Dibucaine and fluoride inhibition is not affected by the presence of the C2 variant.37 Hence, there is no reason to expect any adverse pharmacological reactions in the presence of this variant, so that it can be dealt with very briefly.

(2) Methods of Determination: So far, the variant can be identified only by the electrophoretic means of Harris and his co-workers.36,37

GENETICS

Since terminology threatened to become confusing, a group of interested investigators2 have devised and agreed to the symbols and nomenclature used in the following description.

The letter E is used to designate the gene for cholinesterase, and subscript 1 indicates the first found locus. Then, E1,2 is the gene causing formation of the usual type of pseudocholinesterase; E2,2 is the gene for atypical esterase, and E1,1 causes lack of esterase activity. These three genes are most likely alleles.20 There are then three homo-

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**Table 2. Approximate Prevalence in a Canadian Population of Genotypes in Respect to Pseudocholinesterase**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1,1E1,1</td>
<td>1:100,000</td>
</tr>
<tr>
<td>E1,1E1,2</td>
<td>1:8,000</td>
</tr>
<tr>
<td>E1,2E1,2</td>
<td>1:300</td>
</tr>
<tr>
<td>E1,2E1,1</td>
<td>1:3,500</td>
</tr>
<tr>
<td>E2,2E2,2</td>
<td>1:25</td>
</tr>
<tr>
<td>E2,2E2,1</td>
<td>1:1</td>
</tr>
</tbody>
</table>

See table 1 for symbols. No estimates available for E11 gene.

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1 Discussions have been initiated at the Second International Meeting on Human Genetics, The Hague, September 1963. The complete information will be published.

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TABLE 3. Prevalence of Heterozygotes for Atypical Esterase (Genotype \( E^aE^a \)) in Various Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Number Tested</th>
<th>Number Heterozygotes ( (E^aE^a) )</th>
<th>Percentage</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian (white)</td>
<td>2,017</td>
<td>74</td>
<td>3.8</td>
<td>39</td>
</tr>
<tr>
<td>British</td>
<td>703</td>
<td>27</td>
<td>3.8</td>
<td>40</td>
</tr>
<tr>
<td>German</td>
<td>118</td>
<td>4</td>
<td>3.4</td>
<td>41</td>
</tr>
<tr>
<td>Czechoslovakian</td>
<td>87</td>
<td>7</td>
<td>8.5</td>
<td>41</td>
</tr>
<tr>
<td>Greek</td>
<td>300</td>
<td>13</td>
<td>3.6</td>
<td>40</td>
</tr>
<tr>
<td>Portuguese</td>
<td>170</td>
<td>6</td>
<td>3.4</td>
<td>40</td>
</tr>
<tr>
<td>Moroccan-Jewish</td>
<td>51</td>
<td>1</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>Berber</td>
<td>58</td>
<td>2</td>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td>Mexican Indian</td>
<td>264</td>
<td>7</td>
<td>2.6</td>
<td>43</td>
</tr>
<tr>
<td>Australian aborigines</td>
<td>98</td>
<td>1</td>
<td>1</td>
<td>43</td>
</tr>
</tbody>
</table>

zygotes \( E^aE^a \), \( E^aE^1 \), and \( E^1E^1 \). The first of these has usual esterase, the second has atypical esterase, and the third has no esterase activity. The persons are of phenotype \( U, A \), and \( S \), respectively.

There are the three heterozygotes \( E^aE^a \), \( E^aE^1 \), and \( E^1E^a \). The first of these has usual esterase but a reduced amount on the average. The second has a mixture of usual and atypical esterase, and the third has atypical esterase but a reduced amount on the average. The persons are of phenotype \( U, I \), and \( A \), respectively.

It has been suggested that the gene giving rise to the fluoride type is an allele of \( E^a \), \( E^1 \), and \( E^a \). The gene is called \( E^a \) and is entered as such in table 1. However, some family data to be published make it seem advisable to consider the hypothesis of allelism as not completely established; if the fluoride gene should turn out not to be allelic, it would be \( E^a \), and there would be 18 genotypes instead of the 10 shown in table 1. The poor method of testing makes it difficult to arrive at definite conclusions, both in regard to mode of inheritance and frequency of occurrence. The heterozygotes \( E^aE^1 \) and \( E^1E^a \) led to the recognition for the \( E^a \) gene; \( E^1E^a \) is hypothetical in that the genotype has not been encountered. The homozygote \( E^aE^a \) has been described recently.

As indicated in table 1, six genotypes would suffer prolonged effects of succinylcholine. All heterozygotes who have some usual esterase show an almost normal rate of drug elimination. The reason can be understood on the basis of enzyme kinetics and drug distribution. Any lowering of affinity between succinylcholine and cholinesterase will substantially reduce the hydrolysis rate of the drug, so that a reduction of affinity could be expected to have a much more serious effect than reduction of the amount of esterase.

Only estimates of the combined prevalence of the endangered genotypes can be given but their occurrence might be often as 1 per 1,500. Estimates of prevalence of some specific genotypes in a Canadian population are shown in table 2. As can be seen, \( E^aE^1 \) is one of the most frequently occurring genotypes. Estimates of this genotype have been made in various populations; the data are shown in table 3. For anesthesia, the listed genotype is not important per se but the figures suggest a relatively even distribution also of homozygotes with atypical esterase. The slightly elevated percentage of heterozygotes in the small sample from Czechoslovakia is insignificant but may deserve attention since a Slavic population studied in Canada showed a similar trend.

As has been pointed out, the \( E^a \) variant is not likely of great importance for anesthesia. The gene determining \( E^a \) is not allelic to \( E^1 \) and \( E^a \). Persons with the \( E^a \) variant constitute about 5 per cent of the British population. Among the refugees from Tristas da Cunha, the prevalence of the variant was found to be 17 per cent.
that the level of esterase activity, i.e., presumably esterase concentration, is ordinarily under environmental rather than genetic control.\textsuperscript{44} That means, in spite of all the emphasis on the genetics of pseudocholinesterase, a worthwhile future investigation in this field may be a search for inducers or suppressors of the formation of this enzyme.

**CLINICAL SIGNIFICANCE**

Two widely used drugs are destroyed by pseudocholinesterase, namely, succinylcholine and procaine. In the presence of atypical esterase, the \textit{in vitro} hydrolysis of both agents is retarded.\textsuperscript{11, 19} Nevertheless, atypical esterase is known to have given rise to fatal intoxication with succinylcholine but not with procaine. The main reason seems to be the different clinical application of these drugs.

Procaine is usually injected into tissues at the site of desired action. The most efficient means of extending the duration of action of procaine is to add vaso-constrictors to the procaine solution. Obviously, local absorption influences the duration of action more decisively than does procaine metabolism. Even a slow rate of metabolic conversion may be adequate as long as the drug enters the blood from the depot at a slow rate.

By contrast, succinylcholine is injected intravenously. The largest portion of the injected drug—say 90 per cent to 95 per cent—is destroyed within a minute after the injection.\textsuperscript{4, 31, 35} It follows that only a fraction of the dose reaches the neuromuscular endplate where the drug acts and from where it is gradually dissipated by diffusion into surrounding fluid.\textsuperscript{4} If there is a failure of esterase activity, the neuromuscular junction must be flooded with succinylcholine molecules. Dispersal of this high concentration at the endplate must take a relatively long time, and this explains the prolonged effect.

For persons with atypical esterase (genotype \(E_{1}E_{2}\)), full dose effect-curves for succinylcholine have been determined.\textsuperscript{40} Complete apnea after 100 mg. of succinylcholine ranges from 50 to 65 minutes; double to triple that time may pass until spontaneous respiration is adequate. These apneas are manageable in a well-equipped hospital but real difficulties have been encountered if succinylcholine was given by continuous drip. When a gram or more is used, the apnea may be expected to last for many hours. Recently, two cases have come to my attention where irreversible cardiac failure occurred after several hours of artificial ventilation. Before succinylcholine is used by continuous drip, esterase function should be determined by any of the numerous biochemical methods. If this is not possible, a test dose of succinylcholine should be given, the response timed, and only then should large doses be used.

Vickers\textsuperscript{47} has recently reviewed cases in which the apnea was apparently due to esterase abnormality and yet lasted very much longer than the one or two hours that are

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**Fig. 1.** Death with hyperthermia following general anesthesia. Family tree of affected persons. Circles indicate females, squares indicate males. (From Denborough, M. A., and others: Anaesthetic deaths in a family, Brit. J. Anaesth. 34: 395, 1962.)
maturely because blood pressure started to fall. The patient remained unconscious, his skin felt very hot and sweaty. He received a blood transfusion and was packed with ice. He gradually recovered over a period of one and a half hours. In 1962, he came into the hospital for another operation. He withstood local anesthesia without difficulty.

Inquiry showed that of the 38 relatives of the young man who had had general anesthetics, 10 have died. In all cases, the anesthetic agents were apparently ethyl chloride and ether. The family tree is shown in figure 1. It suggests dominant inheritance of the trait.

In all the cases of death following anesthesia, the course of events has been similar. In all except one, the operation has been minor and successful and so was unlikely to have been the cause of death. Three of the patients have been returned to the ward after operation in an apparently good condition only to die following convulsions about thirty minutes later. In two, the temperature was taken and found to be 43°C and 43°C, respectively.

Speculative attempts at interpretations have been made. The crucial finding in all these cases seems to be the elevated body temperature; if temperature is high, ether is known to produce convulsions, even in animals. Elevated temperatures after anesthesia do not appear to be extraordinarily rare; they evoke a guilt complex in the anesthetist who fears he has caused anoxic brain damage. However, a rise of body temperature is by no means a regular or prominent consequence of cerebral anoxia.

General Anesthetics and Hyperthermia

Denborough and Lovell in 1960 had to anesthetize a young man who came to the emergency ward with a compound fracture. The patient was frightened and stated that several relatives of his had died from ether anesthesia. Fortunately, the authors took the words of the young man seriously. They anesthetized him with particular care, using thiopental, nitrous oxide and halothane. After ten minutes, anesthesia had to be stopped pre-
cutanea tarda hereditaria usually do not require the special attention of the anesthetist.

The disease important in this context is the acute intermittent porphyria. An instructive diagram from the book by Goldberg and Rimington may be helpful for recalling the disease (fig. 2). The diagnostic biochemical feature is persistence of porphobilinogen in urine (fig. 3). Fresh urine is usually normal in color but darkens when left in daylight for a few hours. After standing, the urine might be red enough to suggest the presence of hematuria. Porphobilinogen can be detected easily with the Watson-Schwart test.

Pathologically, the significant lesions are multiple, often segmental, scattered areas of demyelination. This involves mostly peripheral nerves, autonomic as well as sensory and motor. Demyelination of the autonomic nerves will lead to symptoms of abdominal pain and altered gastrointestinal function. Paralysis and sensory loss is explained by damage to motor and sensory nerves. Also, the central nervous system may be affected; psychiatric symptoms occur in a substantial number of cases.

The presenting symptom is most often abdominal pain. Neurologic symptoms of various kinds are the usual reasons to consult a physician in the remainder of cases.

Patients can be free of symptoms for years, perhaps throughout life. They are then usually considered highly strung and nervous individuals. Attacks of clinical symptoms may occur at any time. These attacks can be initiated by administration of thiopental. The most disturbing fact remains that attacks induced or aggravated by thiopental are frequently characterized by paralysis which may take weeks or months to subside or may lead to respiratory failure.

It would be a substantial achievement to understand the biochemical factors that lead a barbiturate to cause persistent paralysis. Solving this question would require full understanding of the mode of action of barbiturates and of the fundamental biochemistry of intermittent porphyria.

**Myotonic Syndrome**

Abnormal reactions of myasthenic patients to various drugs are well known. However, myasthenia, as well as several other diseases affecting muscle function, is not usually a hereditary disease and is, therefore, not discussed. The largest group of genetic disorders are the muscular dystrophies, most of which do not seem to show a special contraindication for anesthetics. However, dystrophia myotonica and the similar myotonia congenita have been singled out for special attention of the anesthetist. These diseases are characterized by a persistence of contraction after a voluntary effort has ceased; for instance, a patient may have difficulty in releasing the grasp of his hand.

Kaufman carefully reviewed anesthesia in dystrophia myotonica. He came to the conclusion that muscular function may be so impaired in advanced disease that respiration is inadequate causing carbon dioxide concentration to increase. Dangers arising from the use of respiratory depressant drugs in patients with marginal respiratory function are obvious. There is no specific susceptibility to thiopental as had been thought but respiration may cease when any depressant is administered; perhaps opiates constitute the greatest danger.

Kaufman mentioned a personal communication to the effect that decamethonium had initiated a generalized attack of myotonia which ended fatally. A dramatic case recently reported by Paterson illustrates the effects of

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Fig. 3. An aid to the diagnosis of acute intermittent porphyria. (From Goldberg, A., and Rimington, C.: Diseases of Porphyrin Metabolism. Springfield, Ill., Charles C Thomas, 1962.)
suxamethonium in a patient who suffered from myotonia congenita of mild degree. Suxamethonium in ordinary doses (0.66 mg./kg.) produced generalized myotonia of all skeletal muscles. The effect lasted for two to three minutes and was not followed by any muscle paralysis. Muscular contraction was so pronounced that intubation or artificial respiration were not possible. The patient recovered without damage.

Familial Dysautonomia

Familial dysautonomia was recognized as a distinct clinical entity in 1949. It is a congenital condition manifested by specific disturbances of the central nervous system, particularly affecting autonomic function. Diagnosis is frequently made when children fail to produce tears when crying. The diastolic blood pressure of children with dysautonomia paradoxically falls when they stand up from a lying position. Other regularly expected features are cold hands and feet; excessive perspiration; disturbed swallowing reflex; poor motor coordination; dysarthria, relative indifference to pain; and emotional lability. So far, the condition has been observed almost exclusively in Jewish children. Family data are compatible with the assumption that dysautonomia is a recessive trait. Cause of the disease might be a metabolic defect. Some failure of catecholamine formation has been found but it is doubtful whether this is the primary defect.

The problems of anesthesia in patients with familial dysautonomia have been described in some detail by Kritchman and associates. The most frequent and serious complication was hypotension, often precipitated by a change of position. Among six cases with severe hypotension during anesthesia, cardiac arrest occurred twice. The experiences suggested that patients with dysautonomia do not tolerate thiopental or tribromoethanol. The authors recommended use of local anesthesia after premedication with chlorpromazine, otherwise use of a volatile anesthetic.

The cyclic vomiting may lead to aspiration and its disastrous consequences. Bronchopneumonia occurred frequently as a postoperative complication.

Sickle-Cell Crisis and Anesthesia

The presence of sickle-cell disease grossly increases the hazards of anesthesia. Sickle-cell disease is due to replacement of the normal hemoglobin A by hemoglobin S. The difference between these two forms of hemoglobin resides in a difference of one amino acid in each of the two beta-chains of the hemoglobin molecule. This small change decreases the solubility of reduced hemoglobin S. Hence, hemoglobin S tends to precipitate within the erythrocyte if there is any anoxia. This leads to distortion of the red cell ("sickling") and often massive rupture of erythrocytes. This crisis may lead to sudden unexpected death from vascular occlusion by thrombosis or infarction, or there may be hemorrhage in vital organs due to increased fragility of the red cells. Massive hemolysis may cause renal failure and anuria with death following a few days after the crisis.

Sickle-cell disease occurs if there are two genes for hemoglobin S, in other words, it is a recessive disease. It is likely a fatal disease but nevertheless may remain undiagnosed for some time. Carriers of the disease are said to have sickle-cell trait. This trait is usually not noticed but in some cases may lead to sickle-cell crises with all the serious consequences that are commonly seen in patients with sickle-cell disease.

A sickle-cell crisis may be precipitated by anesthesia since even a minor procedure is often accompanied or followed by hypoxia. As approximately 7 per cent of American negroes have the sickle-cell trait, the proportion of surgical patients exposed to this special risk is significant.

Miscellaneous Observations

A number of pertinent observations have been previously reviewed so that brief reference must suffice. Other observations in pharmacogenetics are new but can be mentioned only because they are of marginal concern for anesthesia. The following two items are in the latter category:

It had been known for many years that people can be divided into rapid and slow inactivators of isoniazid. Price Evans has
recently shown that the difference is due to lack of a specific transacyclase in the liver of some persons. As a consequence, some people are not able to acetylate such diverse drugs as the chemotherapeutic agentsisoniazid and sulfadimidine, the antihypertensive drug hydralazine (Apresoline), and the psychic energizer phenelzine (Nardil). The observation that all these different agents are affected by this metabolic individuality is still too new to permit full evaluation of the clinical significance.

In a condition called "idiopathic ventricular septal hypertrophy," the septum between right and left cardiac ventricles is so thick that it tends to block the aortic valve. Cardiac enlargement due to incipient failure may under these conditions actually improve the circulation. A dose of digitalis might be fatal if it decreases cardiac size, thus cutting off the blood flow.

Mydriatic agents are generally less effective in dark than in light eyes which has been thought to be due to local factors. It seems, however, that atropine is less active in negroes than in whites, not only on the eye but also upon cardiac rate and on salivation.

Epinephrine reduces intraocular pressure in most eyes but causes an increase if there is a narrow angle between cornea and iris. Since many anesthetics liberate adrenaline, one should therefore expect that intraocular pressure should be elevated for this reason in only some persons and not in others. Also, atropine constitutes a danger only in persons with a narrow angle. However, in the opinion of Dr. Luke, there is a further restriction in that ordinary doses of atropine will be of danger only to the rare persons who are especially sensitive to atropine and have a narrow angle in addition.

In the rare condition of hyperkalemic familial periodic paralysis (to be distinguished from the much more usual hypokalemic disease), Egan and Klein observed extensive paralysis after thiopental. Local anesthetics were used without harm.

Differences in the ability to withstand the stresses of surgery and anesthesia may be associated with differences in cortical size and function that occur between individuals and between ethnic groups.^

Summary

Pharmacogenetics deals with hereditary modifications of the response to drugs. Since there are numerous examples concerning anesthesia, emphasis in this review has been arbitrary. Recent work on the five cholinesterase variants has been surveyed in some detail; effects on metabolism of succinylcholine and of procaine have been compared and consequences of mismanagement discussed. The review includes sections on general anesthesetics and hyperthermia, acute intermittent porphyria, the myotonic syndrome, familial dysautonomia, and sickle-cell crisis. Some further conditions have been commented upon in a section on miscellaneous observations.

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HYPOTENSIVE POLYPEPTIDE

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