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PHARMACOGENETICS

There are many points of contact between pharmacology and other sciences such as physiology, chemistry, biochemistry, and the many branches of clinical science. In recent years closer contact has been established between pharmacology and genetics and a new field for combined endeavour is now indicated by the term pharmacogenetics, for which a better name might have been genetic pharmacology. There are numerous examples of the effects of heredity on drug response in microorganisms, tissue culture, insects and vertebrates, including man. The phenomenon embraces all forms of life because all cells carrying genes are able to respond to drugs and other chemicals. In a recent monograph the existence of hereditary influences on pharmacological responses has been stressed.[1] Pharmacologists and geneticists will do well to study the contents of this timely volume, which brings together much information otherwise only to be found in a great number and variety of journals. The author also indicates which basic books on the two disciplines should be studied, so that each may understand the language and the problems of the other.

A few examples of the effects of heredity on drug responses in man will briefly be mentioned to show the many implications in this field. Here in South Africa it is now common knowledge among scientists that there is a hereditary form of porphyria, different from that form which predominates in Sweden; porphyria was recently the subject of a conference at the University of Cape Town. The local form is transmitted by an autosomal dominant gene, and drugs such as the barbiturates can unmask the latent condition; severe symptoms and even death can occur. Several papers have been published in this *Journal* in recent years drawing attention to this interesting and serious problem.

The potent antituberculous drug, isoniazid, is now established as being more rapidly inactivated by some patients than by others, and this difference in the rate of metabolism is a permanent personal characteristic. Studies have been made on individual patients and on family groups. It appears that the ability to metabolize isoniazid is independent of sex, and that the incidence is not the same in all racial groups. Slow inactivators of isoniazid seem to be more prone to develop toxic effects, but on the other hand have the advantage of responding better to the tuberculostatic effects of the drug. The ability to metabolize isoniazid is dependent on an autosomal dominant gene.

The antimalarial drug, primaquine, can cause haemolytic anaemia in certain individuals. American Negroes have a special susceptibility, and other pigmented races including certain groups in South Africa also show primaquine sensitivity in varying degree. There is a long list of drugs that can cause haemolysis in primaquine-sensitive individuals; besides these drugs, naphthalene and fava beans can precipitate the disease. The chief defect in these subjects is a deficiency or absence of the enzyme glucose-6-phosphate dehydrogenase (G-6-PD), for example in the red blood cells.

Chlorothiazide and related diuretics can produce a variety of side-effects, among which gout and diabetes occur either exclusively or preferentially in persons predisposed by hereditary defects.

Atropine is well known to be dangerous is some persons in whom an attack of glaucoma may be produced. There are some eyes in which the anterior chamber is unusually shallow; the cornea and the iris form a rather narrow or acute angle, which may interfere with the draining of the aqueous humour. This type of glaucoma is probably responsible for less than half of all glaucomata. Much more data are required, but it appears that the depth of the anterior chamber is under genetic control. Incidentally, it is of interest that in mongolism there is particular sensitivity to certain drugs, especially atropine.

Suxamethonium (succinylcholine) is a skeletal muscle relaxant outstanding because of its short duration of action, which results from its destruction by pseudocholinesterase. Prolonged apnoea in many, but not in all, cases is due to a deficiency of cholinesterase. Observations on different types of esterase in different people, and the demonstration that a given type occurs as a constant feature in a particular person, have indicated that there is a hereditary basis for classifying individuals according to their esterase types. This particular problem is presented in great detail in the monograph to which reference has been made. For the fuller details on this and other pharmacogenetic subjects this important volume should be consulted.

1. Kalow, W. (1962): *Pharmacogenetics: Heredity and the Response to Drugs*. Philadelphia: W. B. Saunders Co.

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