Gathered at a conference on Drug Metabolism in Man sponsored last week by the New York Academy of Sciences

DRUG RESPONSE

Genetic effects

To obtain information on the influence of heritable factors on drug response, teams of Boston physicians, since 1967, have been conducting studies of patients at area hospitals, determining individuals' genetic characteristics and evaluating them in light of their response to various drugs. Drs. George P. Lewis, Hershel Jick, Dennis Slone and Samuel Shapiro of the Lemuel Shattuck Hospital report one finding from that program, which has by now included 7,000 patients.

Individuals with low levels of serum albumin, a protein, have an increased incidence of adverse effects from the steroid immunosuppressive drug prednisone, they say. Side effects among these individuals include hemorrhagic complications, psychoses and elevated blood-sugar levels. Persons receiving high doses of prednisone, as expected, had a higher incidence of side effects, but at all dose levels, persons with low serum albumin experienced a greater incidence of adverse reactions than prednisone-taking patients with larger amounts of albumin in their serum.

"The findings of the present preliminary study suggest that in the presence of severe hypoalbuminemia (low albumin levels) the degree of binding of prednisone to serum proteins is decreased, thus allowing a greater amount of the drug to be free and thereby active," they report.

DIGITALIS TOXICITY

Quick test measures drug levels

Digitalis and digitoxin, perhaps the most commonly used agents for control of cardiac irregularities, have one property that distinguishes them from most other types of drugs. The dose at which they are effective is extremely close to the dose at which they are toxic.

Even with careful management, the incidence of digitalis or digitoxin toxicity is about seven percent. A study of Boston patients who were not carefully supervised revealed a toxicity incidence of approximately 25 percent, according to Dr. Edgar Haber of Harvard Medical School. With Drs. Thomas Smith and Vincent Butler, he reports a fast and simple technique for determining levels of these drugs in the blood plasma of patients. The method uses radioimmune assay techniques.

By injecting digitalis and digitoxin into separate animals (rabbits) the scientists obtain serum containing antibodies specific to each drug. In the laboratory, this serum can then be reacted with plasma from patients and assayed to determine the quantity of drug in the patient's blood by measuring amounts bound to the antibodies in an antibody-antigen reaction.

ALLOPURINOL

Inhibiting drug metabolism

A majority of drugs are metabolized by enzymes in the liver. Nearly 200 agents are known to stimulate these enzymes, hence speeding the metabolism of drugs they affect. However, very few enzyme-inhibiting agents are known.

From studies with patients, normal volunteers and with laboratory rats, Dr. Elliot S. Vesell of the Hershey Medical Center in Hershey, Pa., reports that two commonly used drugs inhibit drug-metabolizing enzymes in the liver.

Allopurinol, originally regarded as a drug that specifically inhibits the enzyme xanthine oxidase, inhibits other liver enzymes as well, Dr. Vesell reports. The drug is taken by thousands of patients with gout.

Dr. Vesell administered allopurinol in conjunction with antipyrine, an antifever agent, and found that the length of time the antipyrine remained in blood plasma was longer than when given alone. Studies with nortriptyline, an antidepressant, revealed similar results.

From these experiments, Dr. Vesell concludes that physicans whose patients are taking allopurinol or nortriptyline should monitor their patients for blood plasma levels of drugs, perhaps reducing dosage of the second agent in order to prevent what could be a toxic accumulation in the body.

DRUG METABOLISM

Ingestion versus injection

Biochemically, a drug taken orally does not necessarily behave the same way as it does if administered intravenously. Says Dr. C. T. Dollery of the Royal Postgraduate Medical College in London, "In evaluating drug compounds, all possible routes of administration for clinical use should be taken into account."

Metabolic studies of an asthma compound, conducted by Dr. Dollery and his colleagues, illustrate his point. In an effort to explain the fact that deaths from asthma increased by a factor of three in England between 1960 and 1968, they examined the metabolic fate of isoproterenol, a common antiasthma drug.

When administered intravenously, about 30 percent of a dose of isoproterenol is converted to a somewhat toxic metabolite, 3-0-ethyl isoproterenol. With oral administration, less than 10 percent is so converted.

However, further investigation showed that when the drug is inhaled from an aerosol dispenser (the most common form of administration), about 90 percent of the drug is actually swallowed—in effect, taken orally. Because inhalation therapy involves a dose of approximately 400 micrograms of drug, as compared to only two micrograms in usual intravenous use, patients inhaling overdoses of isoproterenol are actually exposing themselves to large quantities of its toxic metabolite.

Experiments with another drug, propanolol, used by angina patients, showed it is metabolized to 4-hydroxy propanolol when taken orally but that this metabolite does not form when the drug is given intravenously. In this case, both parent compound and metabolite behave similarly, thus avoiding questions of a toxic reaction. However, propanolol's dual fate reinforces Dr. Dollery's point—that scientists should take greater account of metabolic variations according to route of administration.