

The physician at this point scratches his head and says, "Well, this patient may be unusually sensitive to this drug." So he drops the dose to half. And within a few days the blood level is back down, and the patient has lost the toxicity desired. A few days later drug B is stopped and inhibition of the first drug ceases. Now the physician is giving this patient an inadequate dose and the loss of therapeutic effect becomes evident. The importance is realization of the fact that two drugs can modify the effect of one upon the other.

It is a fairly common occurrence, can cause great consternation in any physician, if he does not appreciate this phenomenon. And we are just beginning to appreciate the complexities of drug interactions.

There are several other mechanisms involved, and I will not go into them in any great detail. Occasionally disease of the excretory organ, such as the kidney, can be made worse by a drug. This may cause inhibition of the excretion of another drug, and then drug B (the second drug), will persist in the blood for longer than anticipated periods of time.

Another mechanism is the physical displacement of drugs from blood protein (carriers). Most drugs are bound by circulating proteins, and therefore are relatively ineffective. They only become effective when released from their protein binding sites, and this is again calculated into the dosage requirements. But if you give a second drug that bumps the first drug off of its protein binding site, you will then have more of the free drug A circulating, and in this situation you can get toxicity.

DRUG EXCRETION

A few words about drug excretion seem appropriate. A prototype drug involved in this problem of excretion is phenylbutazone, which is an antiarthritic drug. When given in conjunction with an acetohexamide, a popular antidiabetes drug, the phenylbutazone will inhibit the excretion of the acetohexamide and one can get a higher than anticipated level of the latter. This can cause very low blood sugar levels and occasionally in an elderly patient can cause some hypoglycemic shock.

A drug that is known to inhibit the excretion of penicillin, through blocking kidney reabsorption, is probenecid. This is a drug normally used to accelerate uric acid excretion.

Now, this is a beneficial effect. In this situation we frequently employ penicillin with probenecid, specifically to maintain higher blood levels of penicillin than normal. This is frequently used in patients who have bacterial endocarditis with resistant microorganisms.

RESIDUAL DRUG EFFECTS

Residual drug effects remain another enigmatic area. For example, reserpine, an antihypertensive drug, continues to exert its influence in certain patients for several weeks after it has been discontinued. And it may cause unpredictable responses to general anesthesia. If the anesthesiologist is not very careful, he may get into some difficulty in the process of inducing anesthesia. It is a fine drug, but one must know that it may cause these responses.

In another area, elevated levels of iodine bound to protein were found to persist for 7 years in the sera of women who had received