Gerontological Basis for Modifications in Drug Activity with Age

Sir:

Mann (1) recently reviewed a number of structural and metabolic changes associated with increasing age, and briefly discussed the influence of biological aging on the action of drugs. Variations in drug activity seen in animals of different ages have also been reviewed recently by others (2, 3). While the scope of this review (1) was not intended to include "what might be termed the gerontologic basis for the modification of drug activity," it seems worthwhile to consider briefly this aspect of pharmacology.

A number of factors govern and influence the action of a drug *in vivo*, including absorption, distribution, excretion, and metabolism, as well as the capacity of the receptor site to respond. The over-all response to a drug may also be influenced by a change in the ability of various systems to adjust to its action. The evidence that aging has an influence on each of these factors provides a basis for many of the observed modifications in drug activity.

While data pertinent to the *absorption* of drugs are unavailable, there is evidence that a number of substances, including fat (4) and glucose (5), are less readily absorbed from the gastrointestinal tract, and it has been suggested that drugs are more slowly and less completely absorbed in the older organism (6). There is little information available concerning alterations in drug *distribution* with age. However, systemic blood flow is redistributed (7), and there is a considerable change in small vessels accompanying increasing age (8). As with absorption, it has been suggested that the distribution of drugs is delayed with age (6). In this regard there is a decrease in thyroxin distribution space in elderly subjects which might be related to a decrease in "metabolic mass" (9). Because the percentage of body weight contributed by body fat increases with age (10), the storage and thus duration of action of compounds with high lipid solubility might be expected to be influenced.

The action of a drug is terminated through *metabolic inactivation* (highly lipid soluble compounds) or *excretion* (drugs of low lipid solubility). With age, microsomal enzyme activity is reduced (11) and renal excretory and secretory capacities are limited (12, 13). For these reasons hexobarbital sleeping time is increased with age (14), and higher plasma levels of various antibiotics are achieved (15).

Because of a change in the number of responsible cells in the central nervous system, it has been suggested that the action of stimulants is decreased while the effect of depressants is enhanced (16). Indeed, the central stimulatory action of amphetamine is reduced in the older organism (17), while depressants appear to be more effective (18, 19). Changes in cell or receptor population, enzyme, or substance concentration may also partially explain some of the observed differences in the activity of atropine (20), strychnine (21), alloxan (22), and pentobarbital (23). With increasing age, there is a gradual decline in homeostatic capacity, a situation which is reflected in a limited ability to respond to internal changes induced by drugs. This has the effect of exaggerating the primary as well as secondary activities.

Though the available data are limited, they are sufficient to establish initially a basis for some of the observed changes in drug activity with advancing age. While many of the differences in drug activity are certainly related to the age-associated changes noted above, the *in vivo* pharmacological effect (*i.e.*, lethality) observed is a reflection of each and thus does not permit one to attribute any difference in drug activity specifically to just one of these factors.

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