coupling factor (Bianchi, 1961), it is tempting to assume that an interference with calcium activity may take a part in the mechanism of action of some spasmolytic drugs. On the other hand, the myolytic effect of 2,4-dinitrophenol, ascribed to impaired synthesis of high energy phosphate bonds by West, Hadden & Farah (1951), was not relieved by $CaCl_2$. This fact may account for the lower activity (compared with eupaverin and isoxsuprine) that calcium exercises against papaverine which strongly inhibits oxidative phosphorylation (Santi, Contessa & Ferrari, 1963). Thus, it seems reasonable to investigate whether papaverine may have a dual mechanism of action involving both inhibition of oxidative phosphorylation and an interference with the role of calcium, which is presumably the predominating factor in other spasmolytic agents. Finally the results with isoxsuprine, which is an isoprenaline congener, appear to be in agreement with other findings suggesting that isoprenaline may prevent the entry of calcium into the cell (Schild, 1963).

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Teratogenic activity of drugs

SIR,—Many chemical substances have the power, when administered to pregnant animals, of producing congenital malformations in the young. Methods by which new drugs possessing this action may be readily distinguished are therefore of major importance. By administering drugs initially daily throughout pregnancy and later only during the first trimester, an estimate may be made of the drugs which are most likely to exhibit teratogenic activity in man.

In the course of testing over 40 compounds by this procedure, three types of drug have emerged. Firstly, drugs which kill the mother before any effect is observed on the foetuses; secondly, drugs which kill most of the foetuses before any effect is observed on the mother; and thirdly, drugs which do not kill the mother but which produce changes within the foetuses. As previously suggested (West, 1962), an indication of a teratogenic risk may be obtained by relating foetal resorptions to the doses administered to the mother. When this relationship is made for reserpine, guanethidine and thalidomide (three drugs at one time widely used in human pregnancy), straight line graphs of quite different slopes are obtained. These are shown in Fig. 1. For this work, daily intraperitoneal doses of the drugs were given to groups of 4 rats throughout pregnancy and then to groups during the first trimester. Animals were killed on the 20th day of gestation, and foetal mortality was calculated from the number of live and dead foetuses found. For guanethidine, a horizontal line was obtained since this drug killed the mother before it was lethal to the foetuses. For reserpine, a very steep line was obtained since this drug killed all the foetuses before it was lethal

to the mother. For thalidomide, the slope was very gentle since this drug did not kill the mother and was lethal to only a small proportion of the foetuses.

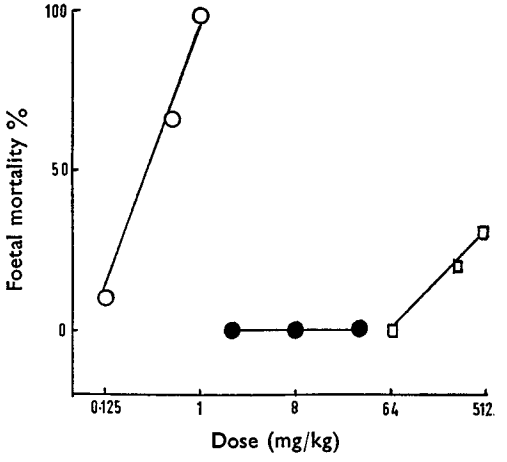

FIG. 1. The relation between foetal mortality and log dose of reserpine (○), guanethidine (●) and thalidomide (□) in rats. The highest doses of guanethidine killed the pregnant rats but did not kill the foetuses.

This last type of effect appears to be more likely to produce congenital malformations in the young since a 10-fold increase in dose produces only a slight increase in lethal action and there is more opportunity to modify the differentiation of tissues in those foetuses which live.

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