Tween 80 to the oil did not result in any greater inhibition than observed in Group 2. There is some experimental evidence to suggest that fatty acids are more potent inhibitors of gastric motility than neutral fats(7). Therefore, one could postulate that the lack of inhibition of gastric secretion by olive oil when bile was absent from the small bowel was due to a lower concentration of products of hydrolysis of neutral fat in the intestinal lumen. However, percentage hydrolysis of neutral fat is often normal in spite of absence of bile salts(8). Furthermore, oleic acid, when administered intraduodenally to intact rats, does not have as strong and as consistent inhibitory effects on gastric secretion as olive oil (unpublished data).

Summary. Gastric secretion in the intact rat is inhibited by fat in the small intestine. This inhibitory activity is decreased when bile has been diverted previously from the small intestine. Under these same conditions, addition of bile salts to administered fat results in the same degree of inhibition as in the intact animal.

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Comparative Plasma Levels of Mephenesin, Mephenesin Carbamate and Methocarbamol.* (25218)

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It has been shown in both animal and man, that significantly higher and more persistent plasma levels were obtained by mephenesin carbamate as compared to those of mephenesin(1,2). When a similar pair of related drugs, namely glyceryl quaiacol ether (G.G.E.) and its carbamate, methocarbamol, were compared by several methods, it was found that methocarbamol gave higher plasma levels than G.G.E. Furthermore, methocarbamol gave higher plasma levels than mephenesin or mephenesin carbamate, following oral administration of equimolar amounts of the drugs to dogs(1). Since similar observations in man have not been reported, it was decided to determine the plasma levels of mephenesin, mephenesin carbamate and methocarbamol, following oral administration of equimolar doses of these drugs to humans. Such studies should be of interest because of clinical reports on the prolonged action of methocarbamol in the treatment of painful muscle spasm(3,4,5,6,7).

Materials and methods. Ten healthy subjects, six males and four females, were chosen. Four subjects (Group 1) were started on methocarbamol, three (Group 2) on mephenesin, and three (Group 3) on mephenesin carbamate. About one week later, when the blood was free of these drugs the subjects of the three groups ingested mephenesin or mephenesin carbamate, or methocarbamol in such a manner as to give randomness in the sequence of ingestion of the drugs. The dosage was 4.00 g of methocarbamol; or 3.75 g of mephenesin carbamate; or 3.00 g of mephenesin. These amounts of drugs are equimolar. The total dose was ingested at once—immediately

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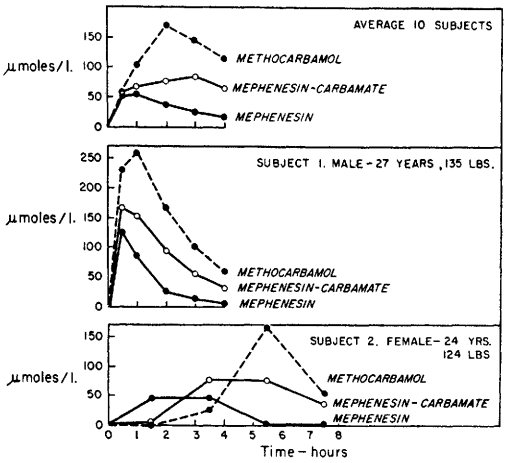

after a control blood sample was obtained. Further blood samples were drawn one-half, one, 2, 3 and 4 hours following the medication. In one subject the studies were repeated and several blood samples were drawn over a period of 7½ hours. After deproteinizing the serum with Folin-Wu reagent, the drugs were extracted with chloroform from an aliquot of the filtrate. The further analytical procedure involved the coupling with a diazonium compound and colorimetric estimation of the complex. In all details we followed the method described by Titus *et al.*(8).

Results. The results of these studies are shown in the accompanying graph. Plasma levels are plotted on the ordinate and are expressed in micromoles per liter of blood because the drugs were administered in equimolar amounts. For comparison on a milligram percent basis, 100 micromoles per liter are equivalent to 2.41 mg% methocarbamol, 2.25 mg% mephenesin carbamate, and 1.82 mg% mephenesin, respectively. In agreement with the observations by London and Poet, it was found that mephenesin carbamate gave higher peak values than mephenesin. Methocarbamol exceeded both drugs in this regard. When the average data (upper part of illustration) were treated statistically, it was found that the differences between methocarbamol on one side and mephenesin and mephenesin carbamate on the other side were highly significant ($P<0.01$), with the exception of the values for the one-half hour levels. As might have been expected, individual differences in the time course of the blood levels were noted. Most subjects gave results as shown in the middle section of the illustration, which are the data of Subject No. 1. Subject No. 2 reacted differently from the others as shown in the lower section of the illustration. When the observation time was extended from 4 to 7½ hours, however, this subject, too, showed that mephenesin carbamate reached higher plasma levels than mephenesin and methocarbamol higher levels than mephenesin or its carbamate.

It is impossible at the present time to interpret the plasma levels of the drugs studied in terms of rates of absorption, excretion and metabolism of the drugs, because of lack of sufficient information concerning these points.

Summary. Ten normal subjects ingested equimolar amounts of mephenesin, mephenesin carbamate and methocarbamol, with intervals of at least one week between medications. Blood levels of drugs were followed for 4 hours, and in one case for 7½ hours. In all subjects mephenesin carbamate gave higher peak values than mephenesin. Methocarbamol exceeded the other 2 drugs significantly in this regard.

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