An adrenergic neurone blocking action of emetine

SIR,—In treating amoebiasis with emetine hydrochloride, some untoward effects are encountered which have not hitherto been explained fully. Prominent among these are diarrhoea and hypotension, both of which appear to reflect diminution in sympathetic tone. The possibility that emetine may exert this effect by adrenergic neurone blockade has been tested by the combined method of transmural and periarterial nerve stimulation described by Wilson (1962).

Segments of guinea-pig ileum, prepared according to the method of Finkleman (1930), are mounted for transmural stimulation (Paton, 1955) in 50 ml of McEwen's solution at 35° and bubbled with 95% oxygen and 5% carbon dioxide. With two sets of platinum electrodes and different stimulation parameters, it is possible to stimulate the parasympathetic cholinergic nerves in the intestinal wall and the periarterial sympathetic adrenergic fibres either independently or simultaneously. Continuous transmural twitches are first obtained with supramaximal stimuli (20 V; 0·5 msec; 6/min), and these are inhibited at 4-min intervals by the simultaneous stimulation of the perivascular nerves with supramaximal stimuli (20 V; 0·5 msec; 50 pulses/sec for 20 or 30 sec). These effects persist in the presence of hexamethonium 1×10^{-4} g/ml, confirming the finding of Wilson (1962).

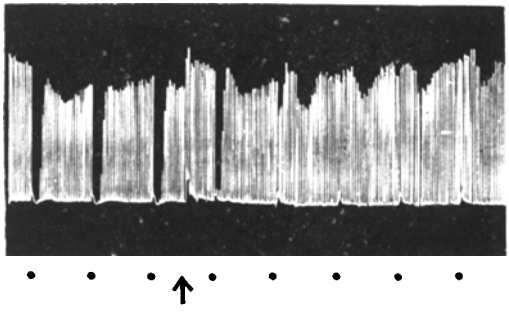

FIG. 1. Guinea-pig ileum. Continuous transmural stimulation (20V; 0·5 msec; 6/min) interrupted at 4-min intervals by simultaneous periarterial nerve stimulation at the dots (20 V; 0·5 sec; 50/sec for 20 sec). Emetine 2×10^{-6} g/ml was added at the arrow indicated. The inhibitory response to periarterial nerve stimulation was abolished and replaced by augmented twitches.

Fig. 1 shows the effect of emetine, 2×10^{-6} g/ml, on the response to cholinergic and simultaneous adrenergic nerve stimulation. The contractions to transmural stimulation are unaffected but the inhibition of these responses by sympathetic nerve stimulation are reduced and finally abolished. In some experiments there is a potentiation of the transmural twitches, and this is not abolished by hexamethonium, 1×10^{-4} g/ml, but is abolished by hyoscine 1×10^{-7} g/ml. When the inhibitory effect of sympathetic nerve stimulation is blocked by emetine, the inhibitory action of added noradrenaline on the transmural contraction is now potentiated. This is evidence that the action of emetine is located elsewhere than at the adrenergic receptor, possibly on the adrenergic fibres.

The evidence also indicates that emetine has no blocking action on the response mediated by cholinergic nerve in the guinea-pig ileum, but that it appears to act on the postganglionic adrenergic neurone interfering with the release of

the sympathetic transmitter substance. This observation may explain the nature of the diarrhoea and hypotension seen in clinical practice.

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Gentisate and guinea-pig testis metabolism

SIR,—Gentisic acid (2,5-dihydroxybenzoic acid) is devoid of uncoupling activity in mitochondrial suspensions (Brody, 1956; Whitehouse, 1964) and does not produce toxic symptoms in large doses in man (Smith, 1952). Claims that gentisate is a therapeutically active antirheumatic drug have been challenged in print (cited in Whitehouse, 1964), but the absence of any well controlled clinical trial still leaves gentisate as one salicylate congener of potential therapeutic value. Recent studies on a liver succinate oxidase preparation (Hines, Bryant & Smith, 1963) and on testis mitochondria (Hines & Bryant, 1966a), both from the guinea-pig, have demonstrated several effects of gentisate on biochemical parameters often greater than those found for the parent molecule, salicylate. These experiments compare salicylate and gentisate effects on the metabolism of radioactive substrates by preparations of guinea-pig testis; and of gentisate on several isolated dehydrogenase enzymes. The tissue was isolated, the fractions prepared and the incubation techniques performed as described previously (Hines & Bryant, 1966b), using 1 μc of each carbon labelled substrate. The radioactively labelled intermediates were extracted with ethanol, separated by two-dimensional paper chromatography, visualised by radioautography and the ^{14}C measured by established techniques.

The results (Table 1) show that gentisate closely parallels salicylate in its effects on preparations of isolated guinea-pig testis. Both drugs decrease the utilisation of (2-^{14}C) - acetate by an homogenate preparation. The qualitative pattern of incorporation of the radiocarbon by each preparation was not altered by either drug. Quantitative relationships were altered, and these are shown as changes in the pool sizes of the amino-acids (alanine, aspartate and glutamate) acids of the tricarboxylic acid cycle (succinate, fumarate, malate and citrate), and those intermediates associated with glycolysis (phosphates and lactate). The inhibitory effect of salicylate on many isolated dehydrogenase enzymes is well established, and the mechanism of the inhibition involves competition with the appropriate coenzyme (Hines & Smith, 1964). The inhibitory action of sodium gentisate (5mM) on several dehydrogenases was also investigated. The inhibitions % (calculated from initial rates) for those dehydrogenases studied are: malate 46, isocitrate 31, lactate (NAD→NADH) 16, (NADH→NAD) 13, glyceraldehyde-3-phosphate 17, α-glycerophosphate 13, glucose-6-phosphate 21. It was possible to reduce the inhibition, in each instance, by the further addition of the respective coenzyme. The interference with transaminase enzyme activity is reflected in the reduced formation of radioactive amino-acids (Table 1) and conforms with established actions of salicylate on both glutamic - pyruvic and glutamic - oxaloacetic transaminase