THE EFFECT OF DRUGS ON THE MOTILITY OF ISOLATED STRIPS OF HUMAN STOMACH MUSCLE

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THE STRUCTURE and nerve supply of the human stomach, the movements of its muscle under a variety of conditions in health and disease, and the effect of various drug substances on gastric activity have been the subject of much research. Carlson[1] and Danielopolu[2] have written extensively on the subject and McSwiney[3] reviews the literature widely. The majority of investigators have made use of a method which records the changes in pressure within balloons placed in the oesophagus, antrum, fundus, pylorus or duodenum of animals or man, or have attempted to assess the alterations in gastric motility by observation and photography with the aid of X-rays. The preparations were all in the fasting state; in some cases contractions of the stomach muscle were stimulated by the previous administration of insulin. Animals might or might not be under the influence of a variety of anæsthetics, or be subjected to ablation of varying portions of the central nervous system. Sundry nerves have been cut and stimulated or allowed to degenerate. From all this work much information has accrued but there has also arisen controversy as to the precise action of a number of drugs of therapeutic importance. One source of error may have arisen from misinterpretation of viscerographic records where the balloon has recorded the activity of the pyloric sphincter when it was supposed to lie in the body of the stomach, or where interpretation of roentgenological observations has been unwittingly influenced by subjective factors during visualisation on the screen.

Apart from the reports of Smith[4] and of Tezner and Turolt[5] very little work has been done with isolated strips of muscle from the human stomach wall, though innumerable experiments have been done with isolated pieces of intestine from animals. It would appear desirable to record the effects of various drugs on isolated portions of gastric muscle before proceeding to investigate and interpret the more complex pictures seen in intact animals and in man. With the recent spread of the practice of partial gastrectomy in cases of peptic ulceration it is now easy to obtain fresh samples of human stomach for investigation.

METHOD

Freshly prepared ice-cold Tyrode solution (sodium chloride 0·8 per cent., potassium chloride 0·021 per cent., calcium chloride (anhydrous) 0·02 per cent., magnesium chloride (anhydrous) 0·001 per cent., dextrose 0·1 per cent., sodium acid phosphate (anhydrous) 0·005 per cent., sodium bicarbonate 0·1 per cent.) was brought into the theatre during operation. As soon as possible after removal of the specimen from the patient, a healthy area of stomach was selected as far as

possible from the diseased area and a portion of stomach wall some 5 cm. square cut off. The mucosa was separated from the muscle layers and the latter conveyed to the laboratory at once in fresh cold Tyrode solution. There a suitable piece of muscle approximately 2 cm. by 1/3 cm. was cut in the long axis of the muscle fibres which is clearly marked, and mounted in the usual isolated organ bath in oxygenated Tyrode solution at 37·5°C. attached to a frontal writing lever. Preparations so mounted showed spontaneous activity of varying degree for 8 to 10 hours; portions preserved at 4°C. could be revived after 24 hours. Drugs were added in solution to make various final concentrations in the 75-ml. bath used. Between tests the preparation was washed twice with Tyrode solution and allowed 15 minutes or more to recover.

Material

The specimens used in this work were from 8 cases of chronic duodenal ulcer operated upon for intractable pain. The muscle fibres used for test were taken from the anterior or posterior wall of the stomach as far from the pyloric region as possible, i.e., the reactions to be described are those of the longitudinal muscle of the body of the human stomach. The stomachs were free from disease in themselves as there was no gastric ulcer or inflammation and no pyloric stenosis or gastric atony or stasis.

The Normal Contraction

Anderson[6] using a viscerographic method describes a phase of relative quiescence characterised by small flat topped waves of about 2½ minutes duration, a phase of active contractions and a phase of tonus waves seen in the course of spontaneous gastric activity and a tetanic phase seen in special circumstances. In the present work all these types of contraction were noted. The tetanic phase only occurs under the influence of an abnormal stimulus such as the addition of a parasympathomimetic drug (see Fig. 1A). The phase of quiescence is the usual finding after the preparation is first mounted and also occurs spontaneously for long and variable periods. It is characterised in the muscle strip by the occurrence of small irregular contractions of some 10 to 20 sec. duration with a return to the base line between each contraction (see Fig. 1A). A modified form of this activity may be found to occur during the period of relaxation between the powerful contractions of the phase of active or hunger contractions (see Fig. 4B) though this is not always the case (see Fig. 2B). The phase of tonus contractions is often found and is characterised by flat-topped contractions of about 2 minutes duration, with variable degrees of relaxation in the course of the wave plateau but no return to the base line (see Fig. 4A). The active or hunger contraction is the most characteristic activity and occurs in spontaneous bursts which reach a maximum degree of contraction after some 10 contractions, continue for a variable period from 5 minutes to 2 hours or more, and cease abruptly or more commonly by declining in vigour to assume the characteristics of the tonus wave or the phase of relative quiescence. Thus

it is seen that the essential characteristics of all the types of wave contraction described by clinical investigators as occurring in the intact stomach of man are to be found in the muscle strip with its absence of circulation, its absence of connection to the central nervous system and its relatively constant environment in a bath of nutrient fluid. It is not suggested that muscular contraction in the normal intact stomach is independent of vascular and nervous influence, but that all the elements for the various types of contraction recorded are available in the muscle and are capable of being carried on by the muscle acting independently. The initiation and regulation of the particular type of contraction found at any one time may well be under the influence of a wide variety of extraneous circumstances.

The Action of Drugs

(a) *Parasympathomimetic compounds.*—Strips of isolated human stomach muscle do not respond to parasympathomimetic drugs in the same low concentrations as do isolated segments of gut from rabbits, guinea-pigs, etc. Acetylcholine in a concentration of 10^{-8} produces only a slight increase in motor activity, but a concentration of 10^{-7} gives rise to a much greater response. If the muscle is in a resting state (phase of relative quiescence) it contracts violently and may pass into a tetanic

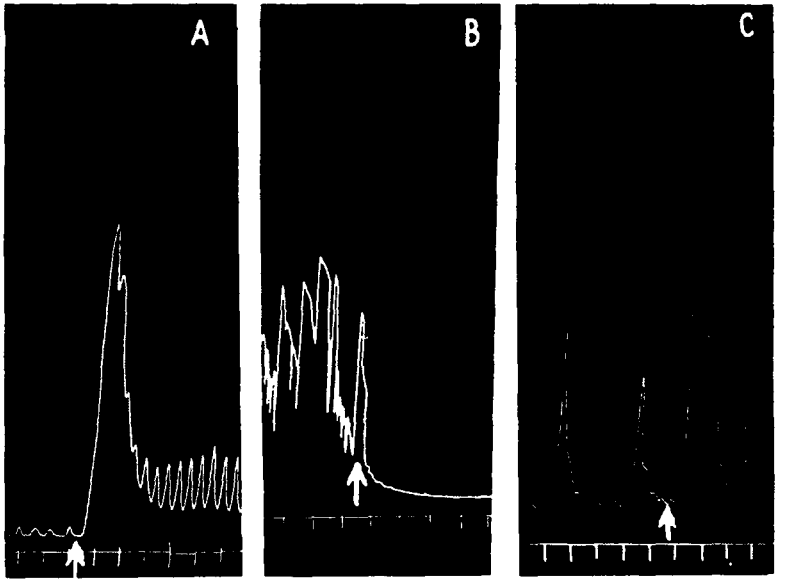

FIG. 1.—Record of movements from a strip of longitudinal muscle from the anterior wall of the human stomach, mounted at 37·5°C. in oxygenated Tyrode solution. Time in 30 sec. 1A shows the phase of relative quiescence changed into a marked motor response and a tetanic spasm by acetylcholine 10^{-7}. 1B shows the phase of active contractions inhibited by adrenaline 10^{-7}. 1C shows phase of active contractions (less violent than in 1B) stimulated by histamine (base) 10^{-6}.

phase (see Fig. 1A). If the muscle is already contracting actively it will pass into a tetanic phase. Carbaminoylcholine in a concentration of 10^{-5}, or eserine 10^{-5} bring about a gradual increase in rhythmic motor activity which may pass into the tetanic phase. The effect of the latter compounds, as in other preparations, is less violent and longer lasting than that of acetylcholine.

(b) *Sympathomimetic compounds.*—Adrenaline in all concentrations relaxes the fibres of the gastric muscle. A concentration of 5×10^{-7} was the greatest dilution which gave definite evidence of activity. If the muscle was in a state of quiescence it relaxed its normal degree of tone under the influence of adrenaline; if it were contracting actively or even in partial tetany all movement ceased and the tone declined. Larger doses up to a concentration of 10^{-7} caused a further degree of relaxation. This

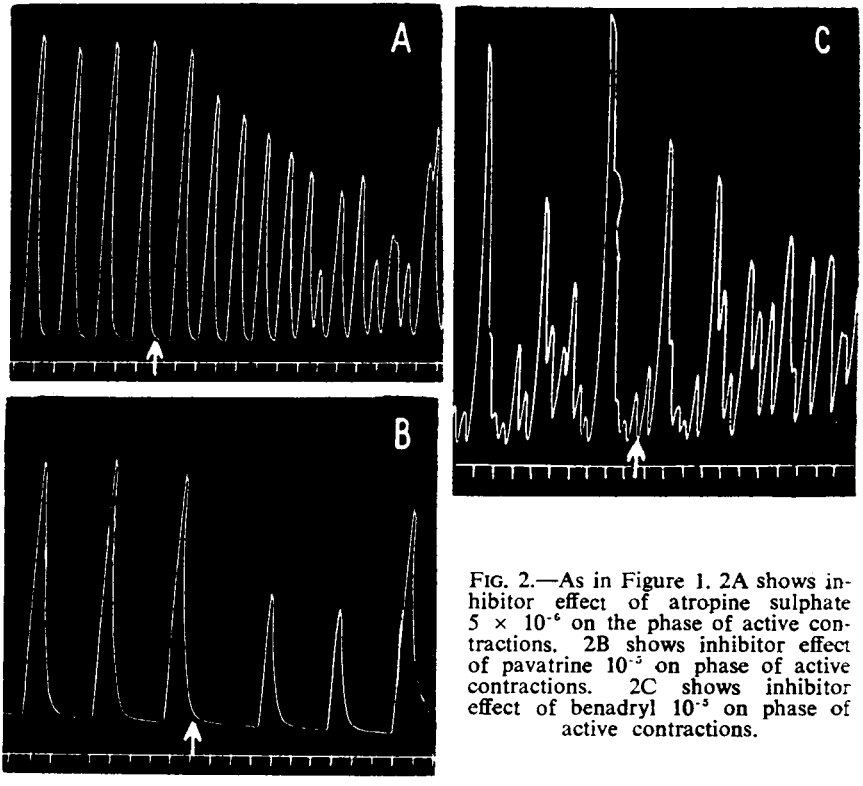

FIG. 2.—As in Figure 1. 2A shows inhibitor effect of atropine sulphate 5×10^{-6} on the phase of active contractions. 2B shows inhibitor effect of pavatrine 10^{-5} on phase of active contractions. 2C shows inhibitor effect of benadryl 10^{-5} on phase of active contractions.

action is shown in Figure 1B. Amphetamine and ephedrine in a concentration of 10^{-5} also inhibit gastric motility.

(c) *Histamine and Barium.*—Histamine in concentrations of 10^{-6} to 10^{-5} of histamine base has a motor effect on the muscle strip. The lesser dose causes a transient increase in contractions, but the larger dose may cause violent contractions and a phase of tetany. Figure 1C illustrates

the effect of histamine 10^{-6}. Barium chloride 10^{-5} also causes increased motor activity of an irregular type and may give rise to tetany.

(d) *Spasmolytic compounds.*—The action of atropine sulphate on this preparation was examined in detail because of the controversy as to whether this drug produces a motor response in certain small doses, as Danielopolu[2] and Anderson and Morris[7] suggest, or is invariably inhibitor in action as Henderson and Sweeten[8] maintain. In the majority of specimens atropine sulphate produced an inhibitor response in all concentrations of the drug which showed any action. If the muscle was in a phase of active contraction the contractions were diminished in extent though they might become rather more frequent. The inhibitory action of atropine in a concentration of 5×10^{-6} on a muscle strip in the phase of active contraction is shown in Figure 2A. Lesser concentrations than 10^{-7} had no effect, and usually 10^{-6} was needed to produce any great degree of inhibition. The activity termed the phase of tonus waves was likewise inhibited by atropine and the action of acetylcholine prevented or abolished. If the muscle was in a phase of relative quiescence the small movements diminished or disappeared.

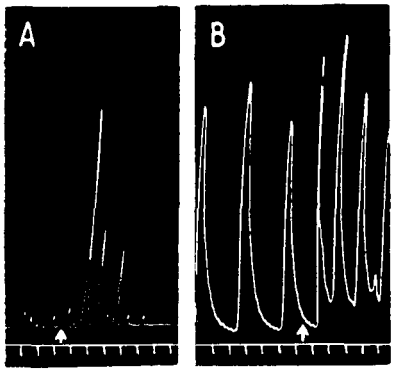

FIG. 3.—As in Figure 1. 3A shows interruption of a long period of relative quiescence by a short burst of active contractions after adding atropine sulphate 10^{-7}. 3B shows the increase in tone and rate of contraction caused by adding atropine sulphate 10^{-7} during phase of active contractions.

In 3 specimens out of the 8 examined atropine sulphate in a concentration of 10^{-7} produced a motor response. This consisted of either a speeding up of the contractions seen in a phase of active contraction (see Figure 3B) with a slight rise in tone, or the production of a short burst of active contractions in the middle of a prolonged period of relative quiescence (see Figure 3A). Further addition of atropine caused inhibition of the stomach muscle, but the effect could be repeated after a period of absence of drug of $\frac{1}{2}$ to 1 hour.

Pavatrine (diethylaminoethyl fluorene carboxylate), which has been shown by Lehmann and Knoefel[9] to have less than 1/20 of the potency of atropine in reducing the hypermotility caused in the stomach of the anæsthetised dog by previous injection of insulin, was active as an inhibitor of contractions in the muscle strip. The concentration required to produce an effect similar to that of atropine 5×10^{-6} was about 10^{-5} (see Fig. 2B). In the small number of tests made on isolated human gastric muscle it would therefore appear that pavatrine approximates more nearly to the activity of atropine than the work of Lehmann and Knoefel[9] on anæsthetised insulin-injected dogs would suggest.

(e) *Anti-histamine Compounds.*—Recently Graham[10] compared the spasmolytic potency of benadryl, neoantergan (2786RP) and antistine. In view of the property displayed by these compounds of inhibiting contractions of gut muscle caused by barium and acetylcholine as well as histamine it is not surprising that a concentration of 10^{-5} neoantergan or of benadryl reduces the extent of the active contraction and the tonus wave of gastric muscle (see Fig. 2C). Benadryl is less powerful than neoantergan in abolishing spasm induced by the addition of histamine but is the more active of the two in inhibiting spontaneous contractions of the gastric muscle.

(f) *Morphine.*—The action of morphine has been the subject of much discussion. Myers[11] working with a viscerographic record of decerebrate cats reported mostly an inhibition of gastric muscle activity with occasional responses by increased movement after injection of morphine. Anderson and Morris[7] working on human subjects reported a diminution of gastric movement followed by a temporary increase and a final state of relative quiescence in fasting patients showing a phase of active contraction.

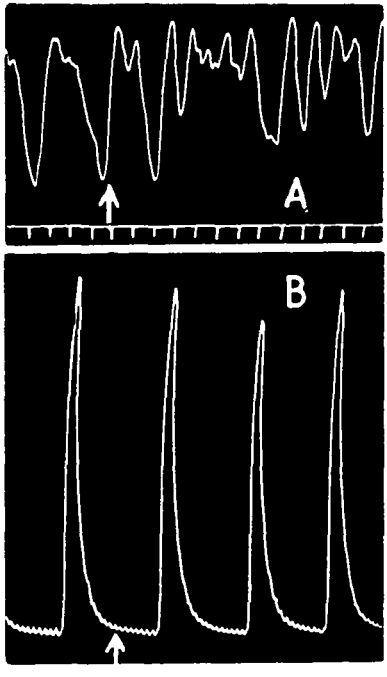

FIG. 4.—As in Figure1, 4A shows increase of tone during phase of tonus wave changes after adding morphine tartrate 10^{-6}. 4B shows the absence of effect after adding morphine 10^{-5} during the phase of active contractions.

With isolated strips in the present work varying effects were obtained. The quiescent muscle and the actively contracting muscle were not affected by morphine tartrate in concentration form 10^{-7} to 10^{-5} (see Fig. 4B). The muscle in tonus waves showed an increase in tone with concentration from 10^{-6} to 10^{-4}. No tetanic spasm was produced nor did the amplitude of the individual wave contractions increase (see Fig. 4A).

DISCUSSION

The statement that the fasting stomach is never entirely at rest is supported by the observation of activity of some sort in isolated strips of human gastric muscle. Hollow smooth muscle viscera with a variable content are seldom at rest. The stimulant action of parasympathomimetic compounds found in this work supports the findings of Smith[4] and Barron[12], and that of histamine agrees with the findings of Schenk[13] while disagreeing with Anderson and Morris[7]. The inhibition of isolated

gastric muscle by adrenaline is in agreement with Smith[4], Tezner and Turolt[5], Dickson and Wilson[14], Barron[12] and Anderson and Morris[7]. It would appear that adrenaline and acetylcholine and their synthetic analogues act in a similar manner upon the isolated gastric muscle as upon the intact stomach in man and in animals. Since histamine is used clinically to promote a flow of gastric juice its action on stomach movements is of some importance. According to Schenk[13] it increases gastric motility (roentgenological studies); according to Anderson and Morris[7] (viscerographic studies) it inhibits gastric activity. Histamine has a motor effect upon a wide variety of isolated preparations of smooth muscle, but not on all. Nevertheless it is unusual for the action to vary in any one species between *in vitro* and *in vivo* preparations of the same type of muscle, especially in the absence of anæsthesia. The dose used by Anderson and Morris[7] was 1·0 mg. per patient, which was less than that used by Schenk[13], who gave 6 to 8 mg. per patient. The latter dose may approximate more closely to that used in the present work (10^{-6} concentration). Both X-ray and viscerographic recording in intact human beings have certain weaknesses, not least of which is the possible introduction of autonomic activity in the patient following upon psychic disturbance as a result of hypodermic injection.

The action of atropine and other spasmolytic compounds is mainly that of inhibition of gastric motility as Bastedo[15] and Henderson and Sweeten[8] claim, but the finding of Danielopolu[2] and Anderson and Morris[7] that small doses of atropine may increase gastric activity is also supported. The nature of this activity is obscure. The differing effects of morphine found with the isolated muscle may help to explain the confusing effects reported by Tolley and Abbot[16], Myers[11] and Anderson and Morris[7].

The general conclusion reached was that the actions of the drugs in common use described were essentially the same in intact patients and in isolated portions of stomach muscle and that the differences observed could probably be explained by complexities in interpretation of recordings from the intact human being, and complexities due to modification of the action of the drugs by influences from the nervous system of the patient (psychogenic and otherwise), influences from the varying content of the viscera, and influences from varying doses and routes of administration of the drugs in clinical use. The beneficial effect of belladonna in the treatment of peptic ulceration may well be explained by the sedative effect of adequate doses of atropine on gastric motility and the blocking effect of this drug on the part played by vagal activity in gastric secretion.

SUMMARY

1. Strips of longitudinal muscle were obtained from the anterior and posterior wall of the human stomach removed at gastrectomy for duodenal ulceration. The preparations were mounted in an isolated organ bath and movements recorded.

2. Spontaneous movement included periods of relative quiescence, periods of slow wave changes in tonus, and periods of active contraction. Periods of tetanic spasm could be induced by drugs.

3. Acetylcholine, carbaminoylcholine, eserine, barium and histamine stimulated the muscle, and adrenaline, ephedrine and amphetamine inhibited it.

4. Atropine, pavatrine, benadryl and neoantergan (2786 RP) inhibited spontaneous and drug induced contractions. Small doses of atropine (concentration of 10^{-7}) occasionally had a motor effect on the muscle strip.

5. Morphine had no effect on the quiescent or actively contracting muscle, but increased the tone of the slow wave of tonus change. Irregularity of spontaneous activity and response to drugs was a marked feature of the preparation.

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