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CHANGES IN INTESTINAL TONE AND MOTILITY ASSOCIATED WITH NAUSEA AND VOMITING

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The general features of the behaviour of the upper parts of the alimentary canal during nausea and vomiting are well known; but the associated disturbances of tone and motility in the intestines have received comparatively little attention. The few recorded investigations do not present a consistent account of the changes which take place, or provide a satisfactory explanation of their cause. The observations and experiments reported here show that in unanaesthetized dogs the nausea and vomiting produced by minimal doses of apomorphine are associated with a definite sequence of changes of central origin in intestinal tone and motility.

METHODS

Healthy adult dogs of either sex were provided with one or two Thiry-Vella loops of upper jejunum by operation under ether anaesthesia with full asepsis. After selection and resection of the required portion of intestine, as close to the ligament of Treitz as convenient, continuity of the gut was restored by end-to-end anastomosis. When two loops were prepared, this was done on a single occasion. About 12 in. of gut was first isolated and then divided at the mid-point. The ends of the two loops so formed were exteriorized in the nipple line on each side of the incision, and the incision closed in four layers.

Records of tone and motility of the loops were taken with the aid of condom rubber balloons of ample size (their diameter when inflated under minimal pressure was about 4 cm.), which were connected by thin rubber tubing to water manometers. The balloons were inflated to a pressure of about 15 cm. water after insertion into the upper end of the loop. The length of each loop was ascertained by allowing the balloon to be expelled from its lower end and then measuring the length of tubing inside the intestine, and this information enabled each balloon to be 'tethered' at about the mid-point of the loop during recording, by means of the wire device depicted in Fig. 1. It makes no difference to the form of the record if the balloon is allowed to move along the intestine, except that there is a considerable rise in tone and the disappearance of contraction waves when it is about to be expelled. If for some reason expulsion is delayed, these changes of motility are prolonged and may be misinterpreted.

The dogs were accustomed to stand quietly in a Pavlov stand during the recording and to receive subcutaneous injections without disturbance.

Considerable freedom of movement—including the movements of retching and vomiting—was permissible without detriment to the record, provided that the dogs were prevented from licking

the ends of the loops, and that the tubing was supported so that its weight, or the movements of the dog, did not pull upon the balloons. Such forms of mechanical stimulation of the loops produced a local inhibition of tone and motility which was transmitted to the other loop and presumably also to the rest of the small intestine, via the abdominal plexuses. This form of 'intestino-intestinal' inhibition has been studied previously (Youmans, Meek & Herrin, 1938).

Nausea and vomiting were produced by means of subcutaneous injections of apomorphine hydrochloride (B.P., U.S.P., British Drug Houses). This method was preferred to such alternatives as distension of the intestine or administration of copper sulphate, digitalis, emetine, carbaminoylcholine chloride, etc., which lack the specific central emetic action of small doses of apomorphine, and may themselves produce intestinal or general systemic effects which would complicate the interpretation of the results.

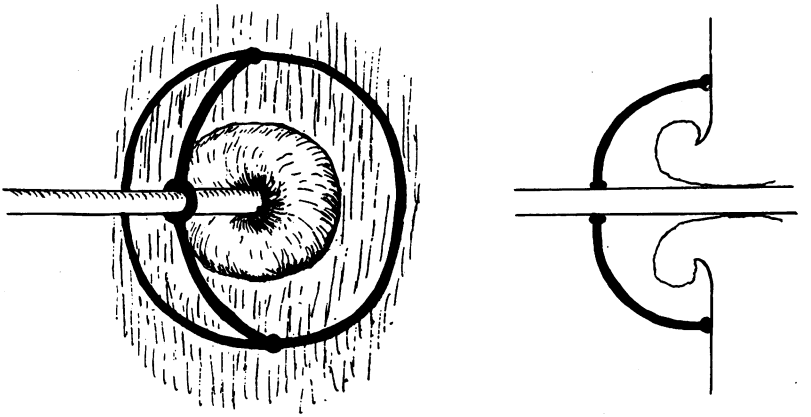

Fig. 1. The wire frame through which the balloon tubing is passed before entering the intestinal loop.

Dosage of apomorphine. It is well known that apomorphine has a depressant effect on the central nervous system of some animals, including the dog, and that samples may be contaminated with toxic impurities or decomposition products (Magnus, 1920). Care was therefore taken to employ the smallest dose which, in a single subcutaneous injection, produced from one to four episodes of nausea and vomiting during the first 30 min. This dose was first found by trial for each dog and then used each time; it varied from 0·02 to 0·10 mg./kg. body weight, and was freshly dissolved in 0·5 ml. of cold distilled water. Only solutions prepared immediately beforehand were used. With this dose, depression and muscular weakness were slight and transient. The dogs recovered quickly and showed a good appetite within an hour after injection.

The earlier observations were made on three dogs which had been provided for other purposes with a single Thiry or Thiry-Vella loop of the upper jejunal region. Four other dogs were each provided with two Thiry-Vella loops of the upper jejunal region. One of each pair was completely denervated at a subsequent operation by stripping from the vascular pedicle all visible nerves and non-vascular tissue for a length of 1–2 cm., a procedure which was followed in each case by the paralytic secretion first described by Claude Bernard (1859). Another noteworthy consequence of denervation was that evidence of visceral sensibility (discomfort on excessive distension or other mechanical stimulation of the loops) disappeared, although it remained in the untouched loop of the opposite side.

The dogs were used for recording about 7–18 hr. after the previous meal; and experiments were carried out in a well-warmed room. If the dogs had not eaten since the previous day, and the room was cold, shivering usually occurred and the records were found to be smaller in amplitude, and the intestinal tone lower, than under more comfortable conditions.

RESULTS

Nausea. After the injection of apomorphine, no effects whatever are apparent on the record of intestinal motility for a few minutes. The contractions continue with their accustomed regularity, at a constant level of tone, the rhythms in each loop being closely similar but not identical. General signs of nausea then appear; they vary a little in different animals, but although not very pronounced with the doses used in these experiments, they are fairly constant in form for a particular animal. The dog becomes subdued and still, yawns once or twice and licks its lips or swallows; salivation may be slightly increased. The respiratory movements are always affected and appear to be the best single indication of the onset of nausea; breathing becomes faster and shallower with the small doses of apomorphine used, though it is slowed and deepened with larger doses. The heart rate is slightly increased and dilatation of the pupils may be observed.

With the first signs of nausea, the tone and motility of both loops are quite abruptly inhibited, and the inhibition may be almost complete in about 30 sec. (Fig. 2). By this time, the tachypnoea is fully developed; and the intestine now shows an equally abrupt increase of tone, with some reappearance of contractions; a 'plateau' of apparently maximal contraction is usually reached and may be maintained for several seconds before a slow decline sets in and normal motility is resumed (Figs. 2, 3).

During this last phase (if retching does not supervene) the respiratory movements also resume their normal rate and depth.

Retching and vomiting. If the state of nausea, instead of subsiding, culminates in retching and vomiting, the rapid shallow breathing accompanying the rise of intestinal tone is seen to change into the slower and deeper respiratory movements of retching. This usually occurs some seconds after the 'plateau' of high intestinal tone has been reached, although where retching and vomiting are repeated in quick succession (Fig. 2) the interval may be short or almost absent. The retching movements, which end in a single powerful effort of emesis, produce synchronous disturbances in both records due to compression of the viscera. Between and after the episodes, intestinal tone and motility continue in apparently normal fashion.

The sequence of events just described has been reproduced with remarkable uniformity in a large number of instances of nausea, retching and emesis, without significant deviation in more than a small proportion of records. Occasionally vomiting is rapid and 'projectile' in character, with little or no premonitory nausea. In these cases the intestinal response may be partly or wholly lacking. The constancy of form and occurrence led at first to the tentative conclusion, subsequently disproved, that the changes were circulatory or mechanical in origin, rather than nervous.

In simultaneous records from the two loops, the observed effects are often closely similar, but never identical in extent or duration (Fig. 2); the only portion of the records in which synchronous excursions occur is during the efforts of retching and emesis. Sometimes the two records differ considerably in the details of the various phases, but the presence of these may almost always be clearly discerned. These observations, together with the fact that

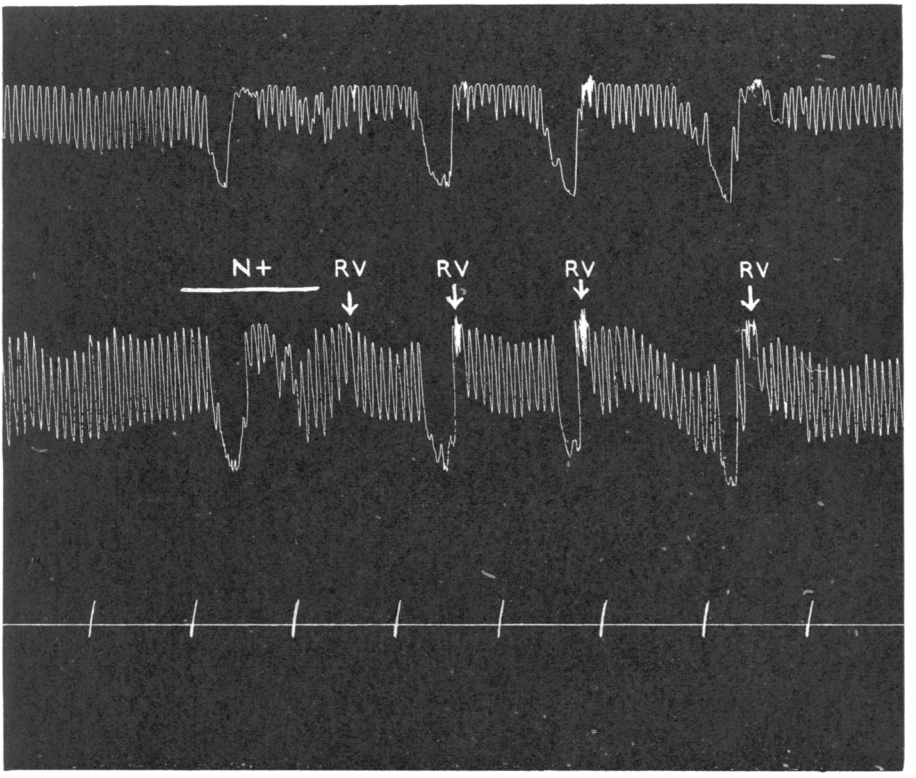

Fig. 2. Simultaneous records from a dog with two Thiry-Vella loops of jejunum. Apomorphine was given 3 min. before the first response shown. *N*, nausea (prolonged); *RV*, retching and vomiting. Time signal 60 sec.

the whole picture of changes may be recorded when nausea alone occurs and when there is no sign of a retching movement, constitute good evidence against the mechanical origin of the changes. The possibility still remains that all the effects described have their origin in some interference with blood-flow through the loops produced by changes in respiration and circulation during nausea, whether or not this is followed by retching and vomiting; further evidence was therefore sought on this point by examining the behaviour of the loops in the two-loop animal after one loop had been denervated.

Effect of denervation. Records were resumed about 7 days after the operation of denervation, by which time the motility and tone of the denervated loop had become apparently normal, while the behaviour of the untouched loop was exactly the same as before the second operation.

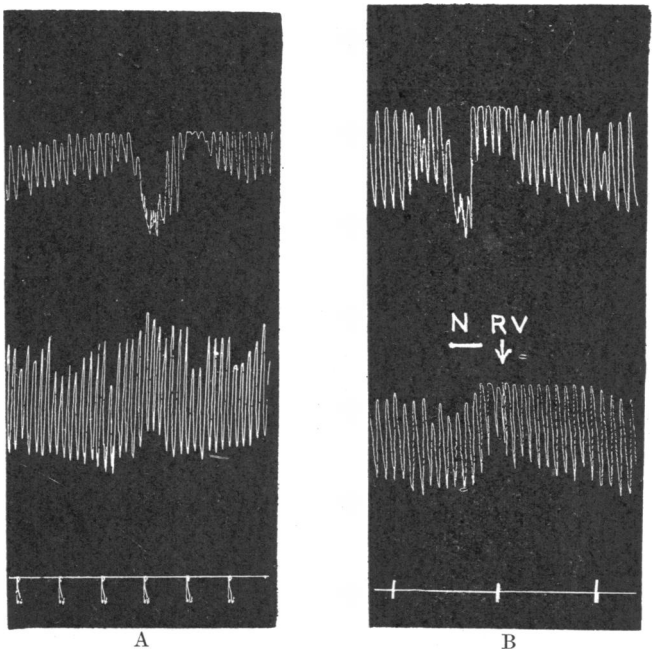

Fig. 3. Records taken from two different dogs, each provided with two Thiry-Vella jejunal loops, one of which had been denervated (lower tracing). Nausea and vomiting produced by apomorphine. A, nausea only; B, nausea (*N*) followed by retching and vomiting (*RV*). Time signal 30 sec. in A, 60 sec. in B.

The results were clear-cut; when nausea and retching occurred, the untouched loop behaved as before, but the completely denervated loop showed no significant changes (Fig. 3 A, B).

In one dog so treated, some doubt was entertained at the second operation as to the completeness of denervation of the pedicle; recording was begun a few days after operation, and the denervated loop was found to show some small and irregular changes in tone and motility, though not the well-defined response recorded at the same time from the other loop. After 7 days it was found that the 'denervated' loop now participated quite definitely in the characteristic changes associated with nausea; and after a further week the response was equally well defined in both loops.

This result, which occurred in no other animal, suggests that denervation had in fact been incomplete, though the remaining nerves were sufficiently interfered with by the stripping to prevent their influencing the loop for some days afterwards.

The results as a whole leave no reasonable doubt that the intestinal response described is due to a nervous discharge along the extrinsic nerves, associated with excitation of the 'vomiting centre' by minimal doses of apomorphine.

DISCUSSION

Babsky (1927) recorded by a balloon method the changes in intestinal activity following the administration of apomorphine to dogs provided with fistulae of the stomach, jejunum and ileum. Strong contractions, interpreted as anti-peristaltic waves, were observed during nausea and vomiting. There are indications in the tracings, on which Babsky makes no comment, that these contractions were preceded by inhibition of the intestine. Oppenheimer & Mann (1941) studied the effects of nausea and vomiting produced by a variety of emetics on the activity of intestinal loops prepared in dogs by Biebl's (1930) method, which preserves intact the blood and nerve supply of the loop, and also the continuity of the intestine. They observed that nausea and vomiting were preceded by marked contractile activity; but owing to the limitations of the recording method necessary with this type of loop, the records give no indication as to whether relaxation of the intestine also occurred. Neither Babsky nor Oppenheimer & Mann provided proof of the origin of the changes observed.

Gruber & Brundage (1935), Slaughter & Gross (1938) and Gruber, Haury & Drake (1939) studied the effects of apomorphine on the tone and motility of the jejunum or ileum of dogs, using similar animal preparations and methods of recording to those used here. Their accounts show a certain measure of agreement with each other in that large and variable changes in tone and motility were observed, which often persisted long after the injection of the drug; the effects observed were assumed to be of peripheral origin, but no proof of this was offered. These findings are in notable contrast to the results of the present experiments, in which tone and motility remained apparently normal after injection of apomorphine, apart from the circumscribed responses associated with nausea and vomiting.

This discrepancy may arise from a difference in the route of administration of the drug. The primary object of the above experiments was the investigation of the action of apomorphine on the intestine, as compared with that of related compounds; and doses of apomorphine often greater than those given subcutaneously in the present work were administered *intravenously*, so that the time course of the concentration of apomorphine in the blood would probably be quite different in the two cases. There is experimental evidence (Hatcher, 1924), which this present work supports, that large doses of apomorphine are comparatively ineffective in producing emesis. For a short time after injection, nausea, retching and vomiting are almost continuous, but then there follows a prolonged period, characterized by depression, muscular weakness and nausea, during which movements of retching and vomiting are infrequent or absent altogether, and cannot readily be evoked by further injections. Further examination of this aspect of the action of apomorphine on the 'vomiting centre' seems very desirable.

Apomorphine has been regularly used in the present work because there is satisfactory evidence of its specific action on the 'vomiting centre' (Hatcher, 1924); but on several occasions the same intestinal response has been observed when nausea and vomiting occurred in relation to stimuli of other types. Distension of an intestinal loop, or the introduction of dilute acid, has sometimes been effective; and on one occasion the whole sequence of intestinal changes described here was observed when a greedy dog was given a large meal while recording was in progress; the animal ate it all very rapidly, and a few minutes later became nauseated and vomited.

The intestinal response described apparently has its origin in an excitation of central autonomic mechanisms, which may also account for several other accompaniments of nausea, namely, salivation, increased secretion of tracheal and bronchial glands, dilatation of the pupils, sweating, pallor, alterations in heart rate and blood pressure, changes in gastric tone and motility (Cannon, 1898; Barclay, 1936), antiperistaltic contractions of the duodenum (Gardiner, 1928; Ingelfinger & Moss, 1942), inhibition or stimulation of gastric secretion (Beamer, Friedman, Thomas & Rehfuss, 1944), and inhibition of pancreatic secretion (Bernard, 1856).

Experiments are in progress to ascertain the nervous pathways involved in the response.

SUMMARY

1. Intestinal tone and motility were recorded by a balloon and water-manometer method from Thiry-Vella loops of the upper jejunum in dogs, and nausea and vomiting produced by the subcutaneous injection of minimal doses of apomorphine.

2. Such doses of apomorphine have no detectable effect on the tone or motility, outside the periods of nausea and vomiting.

3. The first signs of nausea are accompanied by a rapid inhibition of intestinal tone and motility, followed by an equally rapid increase in tone, which may be maintained for several seconds before retching occurs; after this, normal tone and motility are resumed.

4. The response was abolished by denervation of the mesenteric pedicle to the loop; this and other arguments lead to the conclusion that the response is of nervous reflex origin and probably results from the excitation of central autonomic mechanisms.

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