STUDIES ON GASTRIC MOTILITY IN MAN

By

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P R E F A C E

The work on which this thesis is based was carried out in the Department of Materia Medica and Therapeutics, University of Glasgow, and in the Medical Wards and X-ray Department of Stobhill Hospital. The research owes its initiation to Professor Morris who has granted every facility and whose constant help and criticism is greatly appreciated by the author. He also wishes to express his gratitude to Dr.William Martin for his encouragement and permission to conduct the investigation, to Dr.Stanley Alstead for his helpful advice, to Sister Collins of the X-ray Department for her willing assistance with the photography and to Sister Jobson for her constant co-operation in the Wards.

INTRODUCTION

(a) Historical:

The importance of the motor function of the stomach has always been completely overshadowed by the attention paid to secretory activity. This is strange since it is well known that complete achlorhydria can exist without any apparent disturbance of gastric function, whereas normal digestion would be impossible without the peristaltic movements of the stomach. Indeed the general feeling of well-being, characteristic of health, may be banished by some motor dysfunction. An extreme example is post-operative dilatation of the stomach. Less serious types of motor dysfunction are not uncommon; radiologists are well aware of the sudden drop in gastric tone which may accompany the noisy closing of a door.

Until the latter part of the nineteenth century, it was tacitly assumed by physiologists that the stomach was in a state of quiescence unless active digestion was proceeding. Morat, however, in 1882, showed that contractions occurred in the stomach of the fasting unanaesthetized dog, and later made the same observation in man. In 1895, Moritz, using an air-filled balloon, estimated

the difference of intragastric pressure caused by the movements of the diaphragm but made no mention of fasting contractions. Bettman however, in 1899, called attention to the contracted condition of the stomach after a fast lasting several days. Wolff reported in 1902 that after forty-eight hours without food, the stomach of the cat may be so small that it resembles a slightly enlarged duodenum. Boldireff(1904) noted in dogs with gastric fistulae the occurrence of regular rhythmic contractions of the empty stomach and bowel, and that the periods of activity alternated with periods of rest. He found, indeed, that the movements of the empty stomach were frequently greater than those which accompanied digestion. In 1912, Cannon and Washburn put forward the view that the pangs of hunger were associated with the presence of fasting contractions. Washburn was trained to swallow a soft rubber tube with a small balloon attached, which was then moderately distended with air. The apparatus was so arranged that Washburn could not see the recording drum. Whenever he felt a sensation of hunger, he pressed a key which caused an electromagnetic pointer to make a mark on the tracing. These marks were found to coincide with an established gastric contraction. In 1916, Carlson published his well-known work giving a detailed account of his investigations on the fasting

gastric contractions in animals and man. He confirmed the findings of Cannon and Washburn, and in one case reported later,(1918) he demonstrated gastric contractions after a voluntary fast of fifteen days.

Many theories have been advanced to explain the sensation of hunger. Haller(1763) considered that the tonicity and contractions of the empty stomach stimulated the hunger nerves in the mucosa by pressure and rubbing. Erasmus Darwin,(1801) on the other hand, thought that hunger pain was due to the atonic condition and absence of contractions in the empty stomach. Weber,(1846) supported by Vierordt(1871) and Knapp(1905) held to the view that the sensation of hunger resulted from powerful contractions sufficiently strong to reduce the cavity.

No discussion involving the physiology of the stomach is complete without reference to the work of William Beaumont.(1833) From his detailed and painstaking observations on Alexis St.Martin, he concluded:-

> "The sensation of hunger is produced by a distension of the gastric vessels or that apparatus, whether vascular or glandular which secretes the gastric juice and is believed to be the effect of repletion of this fluid".

Carlson(1917) suggested that this theory was untenable on the ground that there was no actual accumulation of gastric juice in the crypts of the glands in the empty stomach to stimulate the gastric nerves by distension.

Boldireff (1905) considered hunger in relation to the periodic activity of the stomach but solely with the idea that hunger might provoke this activity. Brauch, (1938) on the other hand, rejected all theories which made changes in the stomach alone responsible for the hunger sensation, as he found that a feeling of hunger occurred as commonly during a phase of gastric quiescence as during a period of contractions.

At the present time, it is thought that the sensation of hunger is made up of several components of which contraction of the empty stomach is probably one. Cannon (1936) stated that these contractions occurred during sleep; they were stopped by chewing and temporarily inhibited by swallowing. Very vigorous muscular exercise caused a cessation of the contractions but after the exercise was stopped, they might be more intense than before. Patterson, (1914) working on dogs, found that in young animals the fasting gastric contractions were more sustained than in old ones.

The relationship between the contractions of the empty stomach and the movements occurring during digestion have been studied by Rogers and Hardt. (1915) These authors correlated the activity of digestion to the movements of the fasting stomach. Kurzin and Slupsky (1937) have shown that an inflated balloon in the

stomach acting by mechanical stimulation of the gastric mucosa, caused a flow of gastric juice, and that the volume of secretion depended on the area of surface stimulated.

The conditions which produce the fasting movements are not yet understood. Cannon (1936) believed that a reduction of the blood sugar by about 25% led to an increase of gastric contractions, while a rise inhibited them; he concluded that the activity of the muscle fibres of the stomach was related to their need for glucose. Brauch, (1938) however, could find no relationship between the blood sugar level and the occurrence of the fasting contractions. Boldireff and Kellogg, (1929) from experiments on dogs stated that the onset of the contractions of the empty stomach are due to the periodic delivery of pancreatic juice into the duodenum.

(b) The Scope of the Present Investigation:

The original aim was to determine the effects of various drugs on the human stomach. It was soon apparent however from my own experiences, as well as from a study of the previous work that there was some confusion as to the sequence of events in the fasting stomach. It was obvious, therefore, that before any observations could be made on the clinical pharmacology of the stomach some

information had to be obtained on the normal fasting movements. The work opens with an account of the various methods employed in the investigation. This is followed by a section on the interpretation of the tracings and a discussion of the difficulties and fallacies encountered. Gastric motility in health and disease is then described and various reflex phenomena are dealt with in an attempt to throw light on the causation of pain in peptic ulcer. The second part of the thesis is concerned with the clinical pharmacology of the stomach.

(c) The Extrinsic Innervation of the Stomach:

For the purpose of this investigation the view was adopted that the vagus and sympathetic nerves transmit motor and inhibitory impulses respectively to the stomach, i.e. stimulation of the vagus nerve causes an increase in gastric motility; stimulation of the sympathetic reduces motility. This is the simplest interpretation of a large amount of conflicting experimental evidence.

The results from experiments involving nerve section are summarised thus by McSwiney (1931) :-

1. The cutting of one vagus or one splanchnic nerve was without effect.

2. The cutting of both vagi resulted in a temporary dilatation of the stomach associated with delayed emptying and sluggish and shallow waves.

3. The cutting of the splanchnics caused an increase in gastric activity.

4. The cutting of the splanchnics and both vagi caused the stomach to behave as it did after vagotomy alone.

These observations support the view that the vagus increases gastric motility but the sympathetic has an inhibitory effect.

Numerous workers have published their results on the effect of stimulating the extrinsic nerve supply to the stomach. Their results however are contradictory. Thus Spadolini,(1916)(1917) McSwiney(1931) and Alvarez(1940) have described purely inhibitory effects from stimulating the vagus. McSwiney and Robson(1931) have demonstrated that stimulation of the sympathetic nerves caused either contraction or relaxation of the gastric muscle, usually inhibiting the peristaltic waves. Elliot(1905) stimulated the sympathetic nerves and found a loss of tone in the stomach.

In man, however, the few investigations which have been recorded have yielded results favouring the hypothesis which has been adopted in the present work. Exner, quoted by Koennecke,(1922) cut the vagus nerves in tabetics and observed some atony of the stomach. Pieri(1930) reported the results of three bilateral vagotomies in man and found that the stomach had lost some of

its tone. Barron and Curtis, (1937) after bilateral splanchnic section in man, found the periods of activity lengthened. Barron (1937) recently reviewed the literature and gave case-reports of bilateral section of the sympathetic nerves and of the vagus in man, performed for such conditions as severe diabetes and vagotonia. The reports included a study of the gastric activity from observations made with a barium-coated balloon. These results supported the view stated above, i.e. that the vagus nerve carries motor stimuli, but inhibitory impulses reach the stomach through the sympathetic system.

PART 1. GASTRIC CONTRACTIONS IN HEALTH AND DISEASE

S E C T I O N 1.

TECHNIQUE.

Many methods have been described by different authors to obtain tracings of the movements occurring in the empty stomach. In all types of apparatus the same principle is used: a thin-walled rubber balloon is passed into the stomach, and changes in the intragastric pressure are transmitted to the balloon and hence to a recording apparatus.

Carlson(1916) and Brauch(1932) relied on an air-filled balloon which was connected to a water-manometer of U-shape, in which there was a float-recorder. Danielopolu(1930) used a similar intragastric method attached in this instance to a tambour. Weitz and Vollers(1925) introduced both a water and an air-filled balloon into the stomach. In this investigation two methods were employed.

(a) Apparatus Modified from that employed by Carlson. (See Figure 1).

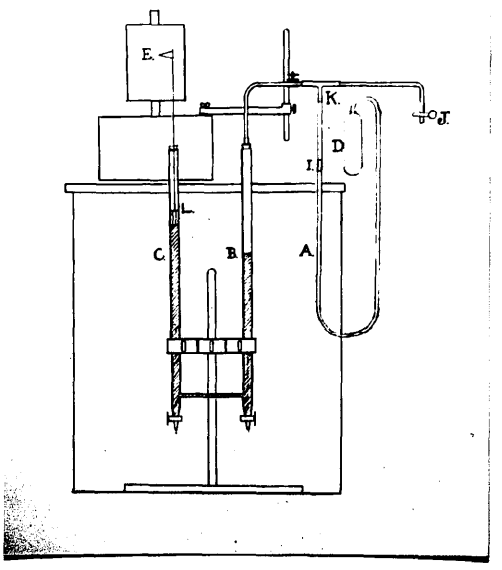


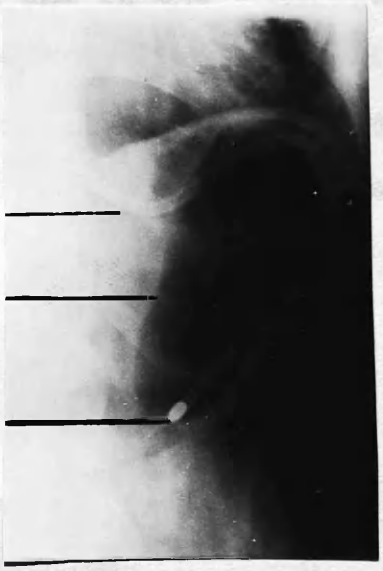
Figure 1.

A Ryle's duodenal tube "A" was taken and a rubber condom "D" of about 200 c.c. capacity was tied to the end of the duodenal tube by means of fine silk thread. The balloon was fixed in such a way that the weighted leaden end of the tube acted as a guide in passing it. The other end of the duodenal tube was fitted to a glass connector piece "I" and then to the vertical limb of a T-piece "K". To the outer horizontal portion of this T-piece was attached a small length of rubber tubing with a clamp "J" compressing it. This was used as the valve controlling the supply of air to the balloon. From the inner horizontal part of the T-piece there was a rubber connection to a burette "B", which was attached to a side-piece at its lower end to a second burette "C" of equal diameter. The burettes formed a U-tube, and were filled with water to a specified mark. The water assumed the same level in both burettes. A vulcanite float "L" was introduced into the second burette "C", so that it moved accurately with any change of level of the water. A recording point "E" on the upper end of the float was kept in contact with the smoked paper of a slowly revolving electric drum "H" while a time-recorder "F" worked by a Brodie's clock was used. (See Figure 4). The deflated balloon was swallowed until the mark 60 (midway between marks ii and iii) was between the teeth of the patient. Air was then introduced

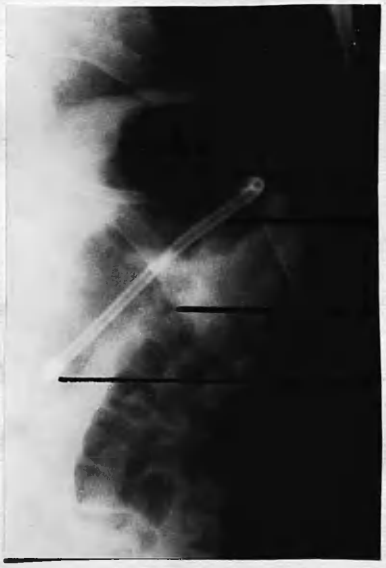
until the level of the water had moved down 5 c.c. in burette "B". As the burettes used in this method were both of the same diameter (1.2 cm.), there was a difference of water level of 10 c.c. in the burettes. After the balloon was inflated a period of fifteen minutes was allowed to elapse so that the patient could become accustomed to the experimental conditions. In this interval, an x-ray screening examination was performed in order to obtain accurate information as to the exact position of the balloon. Manipulation of the tube, if necessary, was then carried out, after which the tube was fixed by adhesive tape to the patient's cheek.

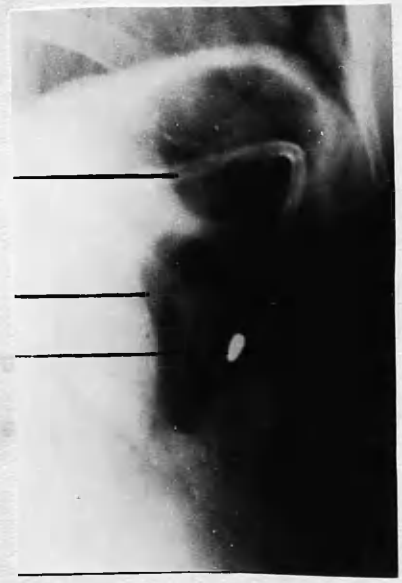
After the experiment was completed, the clamp on the U-tube was loosened and the air allowed to come out of the balloon so that the tube could be withdrawn.

With a little practice, the deflated instrument was swallowed without difficulty by most of the patients. The balloon produced no discomfort and no difficulty was experienced by the patient in keeping at rest. The recording was always taken with the patient sitting upright in a hard chair because a comfortable chair frequently induced sleep. The investigation was usually carried out in the afternoon, the patient having had a light breakfast and no lunch, - the average fast being five hours.



A. Balloon is seen in resting stomach.





B. and C. demonstrate the position assumed by the balloon in the contracting stomach.

Figure 2.

X-ray photographs shown illustrate the position of the balloon in the resting and in the contracting stomach (Figure 2). A few tracings were taken with a small finger cot balloon of 20 c.c. capacity using burettes of equal internal diameter. One such recording is shown here. (Figure 3).

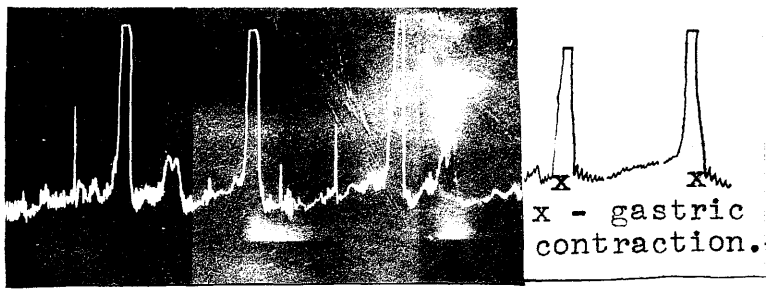


Figure 3.

This procedure was abandoned in favour of a method using a larger 200 c.c. balloon and it was thought that this gave a much more accurate interpretation of events occurring in the stomach.

(b) Apparatus Modified from that employed by Brauch. (See Figure 4).

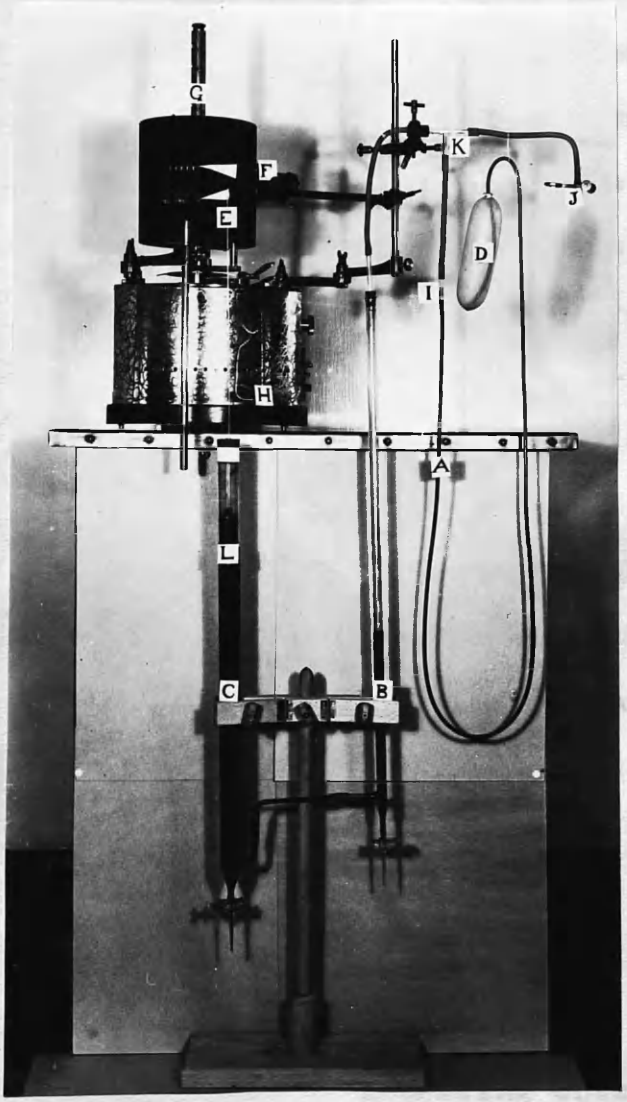


Figure 4.

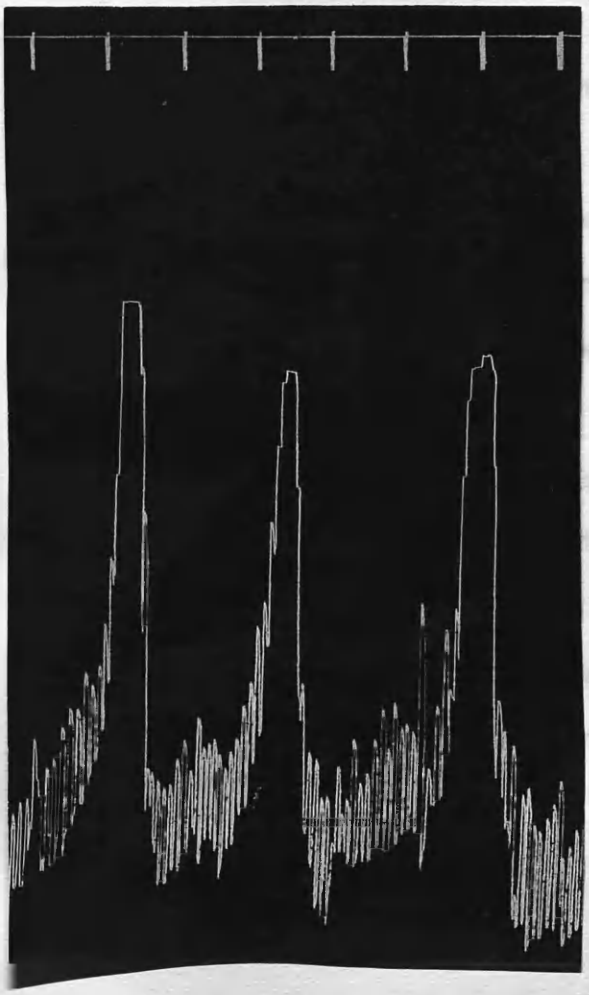
The second method used was a modification of that described by Brauch (1932). This author favoured a small balloon but a large one was used in the tracings shown here.

The apparatus corresponded exactly in principle to that described above. The main difference was that in this method, the bore of the two burettes was different: burette "B" had the same bore (1.2 cms.) as in the previous method but burette "C", which contained the recording float, had a much wider internal diameter (2.5 cms.). This change in diameter necessitated the use of a celluloid float. An increase in the intragastric pressure now produced a different response in the two burettes owing to the difference in bore. A fall of water-level of 6 c.c. in burette "B" caused the float in burette "C" to rise only 1 c.c. This had the effect of eliminating minor oscillations of the recording point, and enabling a much clearer tracing to be obtained. In this method, the preliminary steps quoted above were performed and air was introduced into the intragastric balloon until the water-level in burette "B" had moved down 5 c.c. This figure was kept constant for each recording.

As described above, apparatus modified from that employed by (a) Carlson and (b) Brauch was used in this work. Small portions of a tracing obtained by each method are shown. (Figure 5). Marked difference in the amplitude of the waves is seen and with the modified Brauch's technique a considerable damping down of extraneous oscillations is noted.

The strip of smoked paper used on the drum was about eighteen inches long. These tracings were therefore photographed in order to obtain records that could be included in the thesis. If the apparatus employed was that modified from Carlson, the tracing was marked "Method A." Similarly, "Method B." stands for the modification of Brauch's apparatus.

Method A.



Method B.

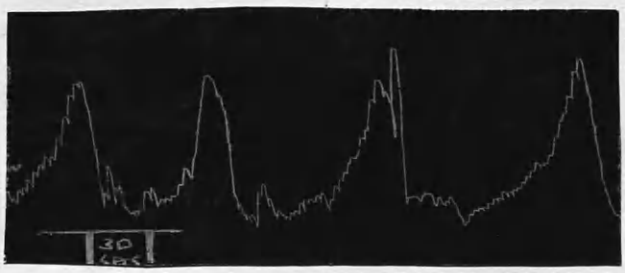


Figure 5.

Fear and excitement interfered with the normal gastric contractions. Thus any patient, showing signs of emotion during the investigation, was considered unsuitable and excluded as a subject in the present research. The Ryle's tube was passed with the balloon completely deflated. In every case, the patient was made familiar with the procedure by frequent practice with an ordinary stomach tube. The actual passing of the tube was so arranged that the first swallow enabled the patient to get the lead guide into the upper part of the oesophagus. The patient was encouraged to swallow the tube at the first attempt and was urged to swallow the tube slowly and naturally but at no time was the tube pushed down. The best lubricant for the tube was found to be sterile water, since some patients were nauseated by liquid paraffin. Special care was exercised in tying the rubber balloon to the Ryle's tube because if the connection was faulty, it assumed on inflation a position at right angles to the tube. This was found to be the commonest cause of the condom folding upon itself inside the stomach and was avoided by ensuring equal puckering of the condom where it was attached to the Ryle's tube.

S E C T I O N 2.

INTERPRETATION OF THE WAVE OBTAINED

Except that the amplitude of the waves is different, the tracings obtained by the two methods described above are identical. Several characteristic features can be made out.

1. The Respiratory Movements:

The small frequent oscillations represent changes of intra-abdominal pressure due to respiratory movements. The accompanying tracing shows the wave from the stomach compared directly with the respiratory movements taken by a stethograph. It is seen that the small regular oscillations of the two tracings coincide. (Figure 6).

Method A.

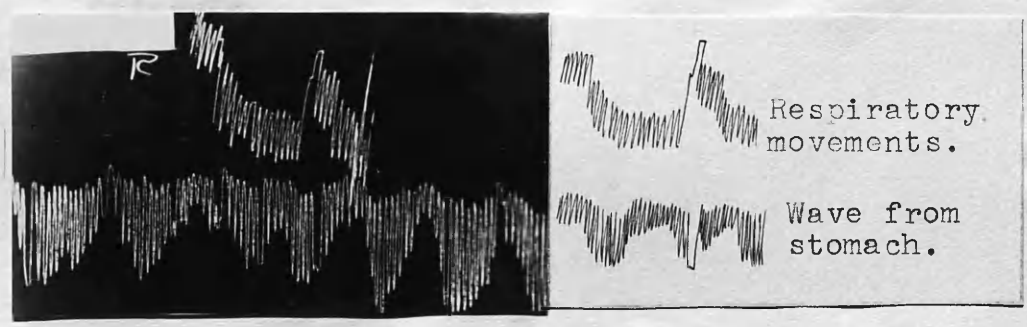


Figure 6.

2. The Pulse Tracing:

Occasionally there is apparent a small notch occurring in the respiratory wave. This represents the cardiac impulse as received from the pulsation of the aorta in the abdomen. (Figure 7.)

Method A.

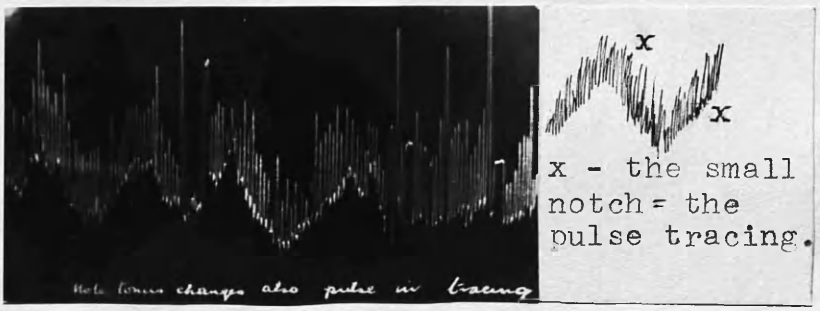


Figure 7.

3. Waves due to Changes of Intragastric Pressure:

These are of three types:-

(a) The true gastric contraction is represented by a sharp-topped wave lasting 30 to 40 seconds.

(b) A less abrupt regular wave lasting about 90 seconds represents a slow rise and fall of intragastric pressure.

(c) Lastly, careful inspection reveals periodic undulations which occur even when the stomach is apparently at rest. This may be called the phase of relative quiescence.

4. Waves due to Changes of Intra-abdominal Tension:

At times other phenomena are noted:-

(i) A sharp-topped irregular wave of shorter duration than 30 seconds usually caused by the patient sighing or yawning may be found. This occurs suddenly and does not fit in with the phase of gastric motility under observation.

(ii) Irregular waves of varying shape, due to movement on the part of the patient such as bending down, or crossing the legs, may occur.

SECTION 3.

THE EFFECT OF THE BALLOON ON GASTRIC MOVEMENT

Control Observations

Cannon(1911) quoted Moritz(1895) who suggested that the presence of the balloon inside the stomach merely elicited the contractions associated with the presence of a foreign body. Carlson(1916) refuted this suggestion and Neidhart (1935) declared that the activity of the empty stomach was not significantly affected by the presence of the condom. No absolute proof has been presented however that the balloon does not act as a foreign body, but my own observations provide scant support for Moritz's suggestion. When the condom is in position and inflated to its usual size, no movement of the stomach beyond the flat waves of relative quiescence may be seen for periods of two hours at a time. It is fair to assume that if the balloon acted as a foreign body these long periods of rest would not occur. Occasionally tracings show a very short phase of contraction followed by a long period of rest. This seems to indicate that after the initial disturbance due to inserting the balloon, mechanical stimulation diminishes

and soon becomes insignificant.

A slight increase in the air pressure of the balloon within the stomach produced no change except a rise in the level of the whole tracing with more marked respiratory oscillations. (Figure 8). Danielopolu(1930) stated that such increase in the tension of the balloon was commonly followed by the onset of tetanic contractions: I have been unable to confirm this.

Method A.

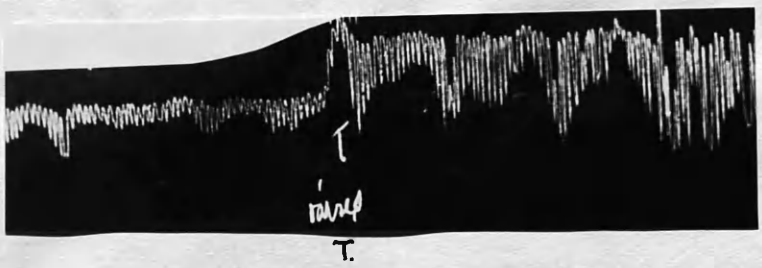


Figure 8.
At T. the air pressure in the balloon was raised.

Objections have been raised by Alvarez(1940) who considered that the movements found with the balloon in situ were artifacts. He suggested that the least distension of the condom would serve to increase the amplitude of the little movements which were constantly taking place. To elucidate this question, Gianturco(1934) outlined the two curvatures of the stomach in cats, by

inserting small shot under the serosa. By means of roentgenologic motion pictures, slight rhythmic movements of the stomach were seen. It seems probable, however, that although the x-ray method may show only little movement, the changes in intragastric pressure may be more marked.

Other observers, too, have found fasting movements in the stomach when there was no balloon present. McSwiney and Spurrell,(1933) by outlining the gastric walls with silver sutures found waves passing over the fasting stomach of dogs. Templeton and Johnson(1929) showed activity in the fasting state without the use of a balloon by recording the pressure in the gas-bubble of the stomach.

It is concluded that the balloon itself does not cause contractions. On the other hand, it is possible that the normally occurring contractions are magnified by the presence of the balloon.

SECTION 4.

DIFFICULTIES and FALLACIES

During the course of the investigation it was found that movements were recorded which were independent of those due to gastric contractions. It was essential for the proper interpretation of any tracing that the origin of these extrinsic movements should be established.

(a) Movement of the Patient:

The patient should as far as possible sit still throughout the experiment as body movement often results in the appearance of sustained flat-topped waves in the tracing.

(b) Cough:

A frequent cough renders a person unsuitable for investigation of gastric motility by these methods. The sharp sudden rise in intra-abdominal pressure produced by a cough may simulate a gastric contraction and constant observation is necessary to exclude this fallacy. If the cough is severe, the marking point is usually thrown off the recording drum, and it is impossible to draw any conclusion from the tracing. (Figure 9).

Method A.

X

At X the recording pointer was thrown off the drum by the force of the cough.

Figure 9.

(c) Sighs and Yawns:

When an investigation lasts two to three hours, it is inevitable that some subjects should develop fatigue and boredom. If the patient then yawns or sighs, the marking-point on the tracing is seen to rise and fall rapidly, producing a wave which is always of less than thirty seconds' duration.

(d) Hiccough:

In one case, a series of sharp sudden waves occurring one immediately after the other was found. (Figure 10).

Method A.

Figure 10.

No explanation of this was apparent until it was noted that the patient had developed hiccough. Here again the fallacy is obviated by keeping the patient under continuous observation.

(e) Unsuitable Preparation of the Patient:

In order to obtain accurate information concerning the fasting contractions of the stomach, the patient must be suitably prepared for the investigation. No food should be taken for at least five hours before the experiment is started. It is also necessary to gain the patient's confidence and enlist his full co-operation. If he is excitable, it is useless to proceed with the investigation, as control observations cannot be obtained under these conditions. Carlson (1916) has shown experimentally

that a slight febrile illness, for example, a common cold, interferes with gastric motility. In this connection it is interesting to note that as long ago as 1833 Beaumont noted that hunger disappeared completely during febrile illnesses. In the present investigation, a patient with slight coryza was observed for a period of two hours, without the occurrence of a gastric contraction. The same patient normally had at least twenty gastric contractions during a similar period of observation.

(f) Oesophageal Contractions:

In order to make sure that the balloon is actually in the stomach and not lodging in the oesophagus, it is necessary to check the position by x-ray examination at the beginning of every investigation.

Method A.

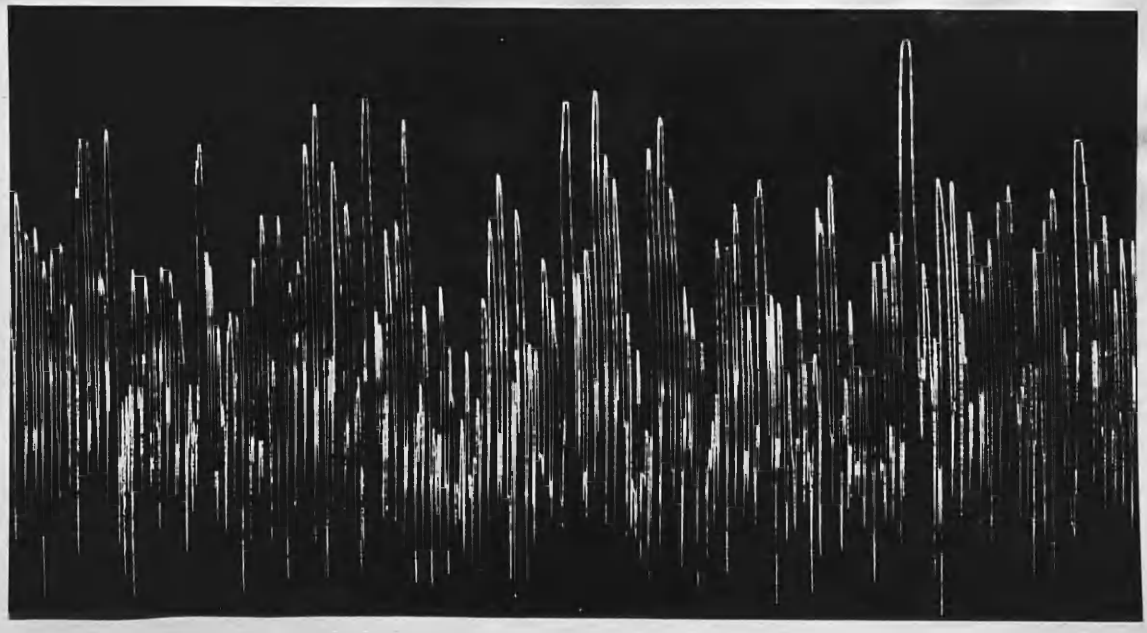


Figure 11.

Figure 11 is an example of the type of wave seen when this occurs. Very marked respiratory excursions are found and the tonus changes in the oesophagus are exceedingly difficult to interpret. The fallacy is avoided if the balloon is deflated and passed further down into the stomach. Figure 12 shows an x-ray photograph of the balloon in the oesophagus.

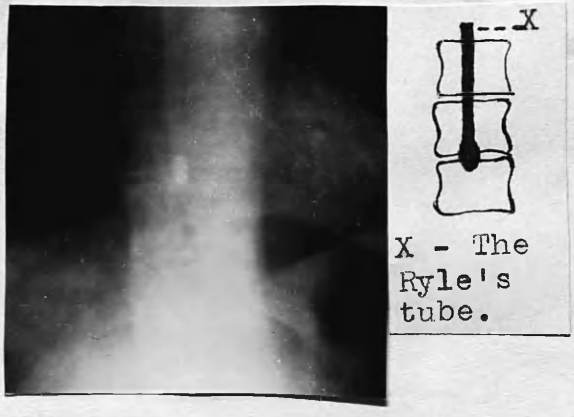
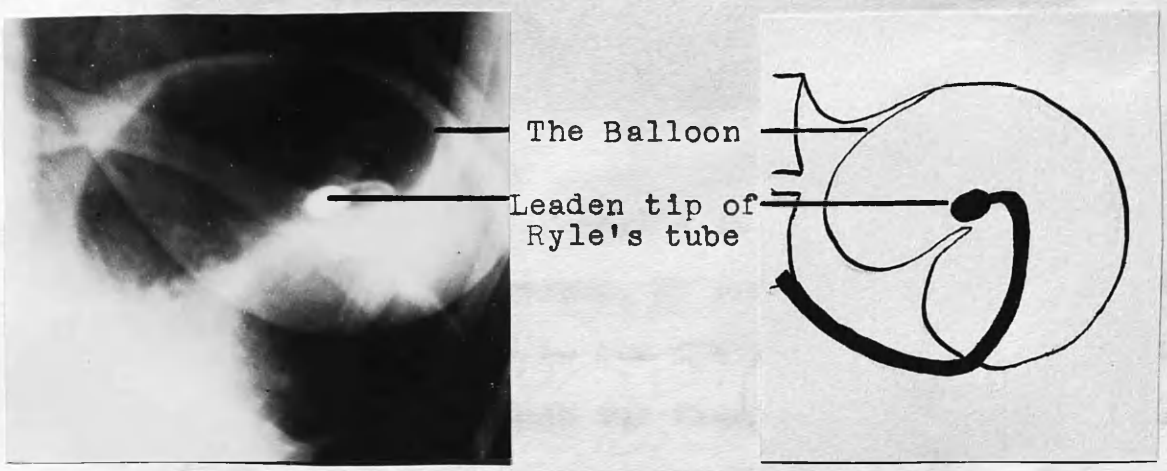


Figure 12.

(g) Folding of the Balloon:

As a rule, a large condom (200 c.c.) was used. Once the balloon was in the stomach there was rarely any difficulty. Brauch (1932), Weitz and Vollers (1925) used small balloons. It is possible, however, that the position of these balloons in the stomach may have varied greatly.

On several occasions, in the present work, it was found that the large balloon had folded upon itself. (Figure 13). In this position readings are obtained only from the fundus. (Figure 14).



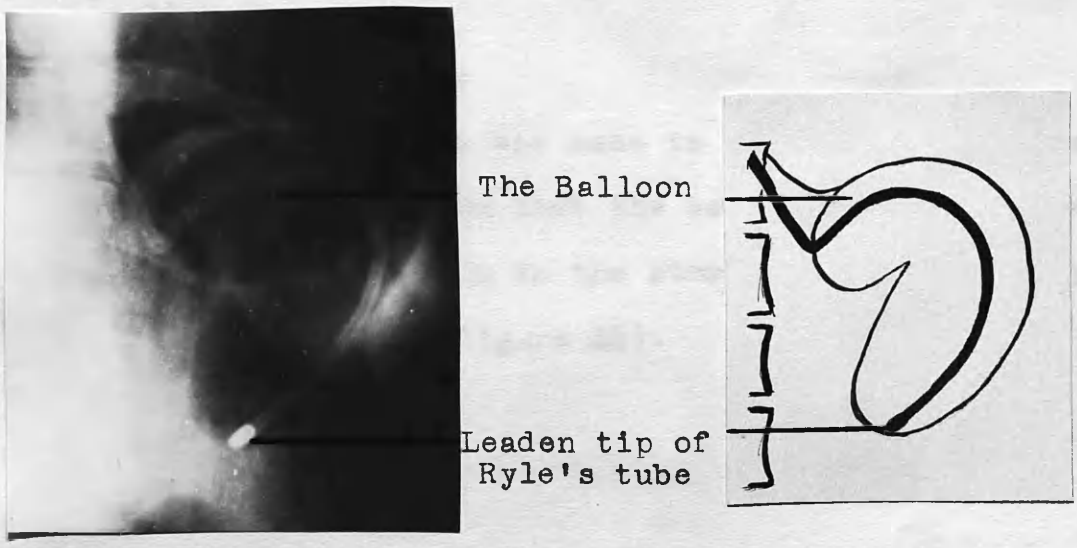
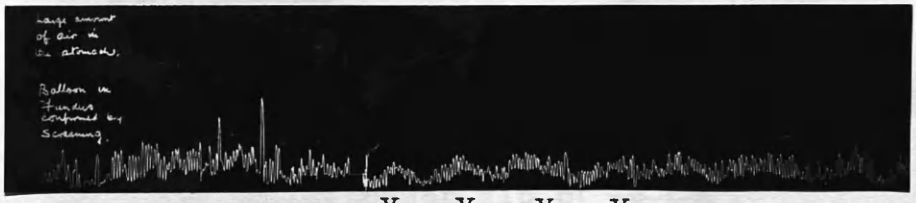


Figure 13.

Method A.



Y. Y. Y. Y.

Y. = Tonus waves.

Figure 14.

In one patient, it was found possible to adjust the deflated balloon to the correct position but on inflating it, the balloon was found to have assumed a horseshoe shape, and to be situated in the fundus. Frequent attempts to change the position by deflation and re-inflation proved unsuccessful. Repeated screening is necessary to confirm the position after the balloon has been swallowed.

(h) Aerophagia:

An attempt was made to investigate this condition, but it was soon found that the balloon would not assume a satisfactory position in the stomach while air was present in large amount. (Figure 15).

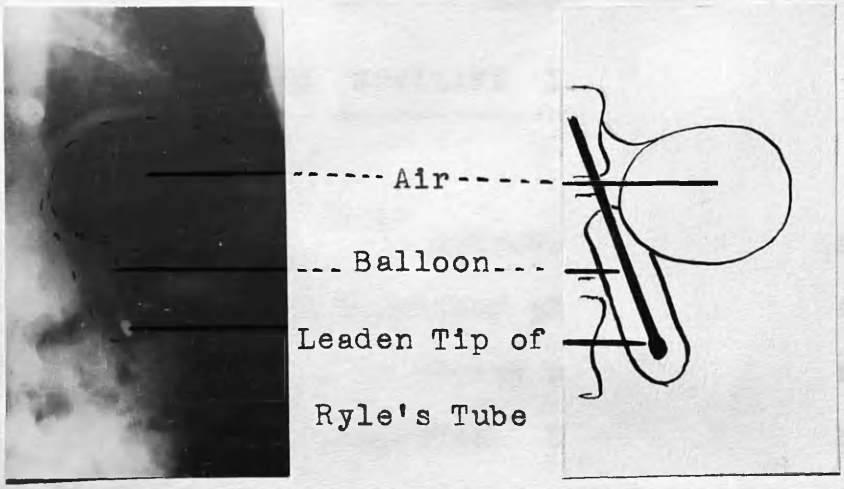


Figure 15.

Repeated attempts to withdraw the air with an electric pump were unsuccessful. The balloon method of investigation of aerophagia was therefore abandoned.

S E C T I O N 5.

GASTRIC MOTILITY IN HEALTH.

Boldireff[1904] introduced balloons into gastric fistulae in dogs and described phases of activity varying in length from twenty to thirty minutes with periods of rest of 1½-2½ hours' duration. Cannon and Washburn[1912] found that the periodic activity of the stomach in man was very similar to that occurring in dogs. They found that each contraction lasted thirty seconds and that there was an interval of from thirty to sixty seconds between contractions. Weitz and Vollers,[1925] Brauch,[1937] Danielopolu,[1930] and Barron, Curtis and Haverfield,[1936] have also described these fasting movements. The fullest account is that given by Carlson[1916] who classified the phases of activity of the empty stomach thus:-

I. Periods of powerful rhythmical contractions alternating with phases of relative quiescence. Each individual contraction lasted thirty seconds.

II. Tonus rhythm (tonus contraction of the fundus). These waves were always present, had a duration of twenty seconds, and fluctuated in amplitude.

III. Pulse pressure rhythm.

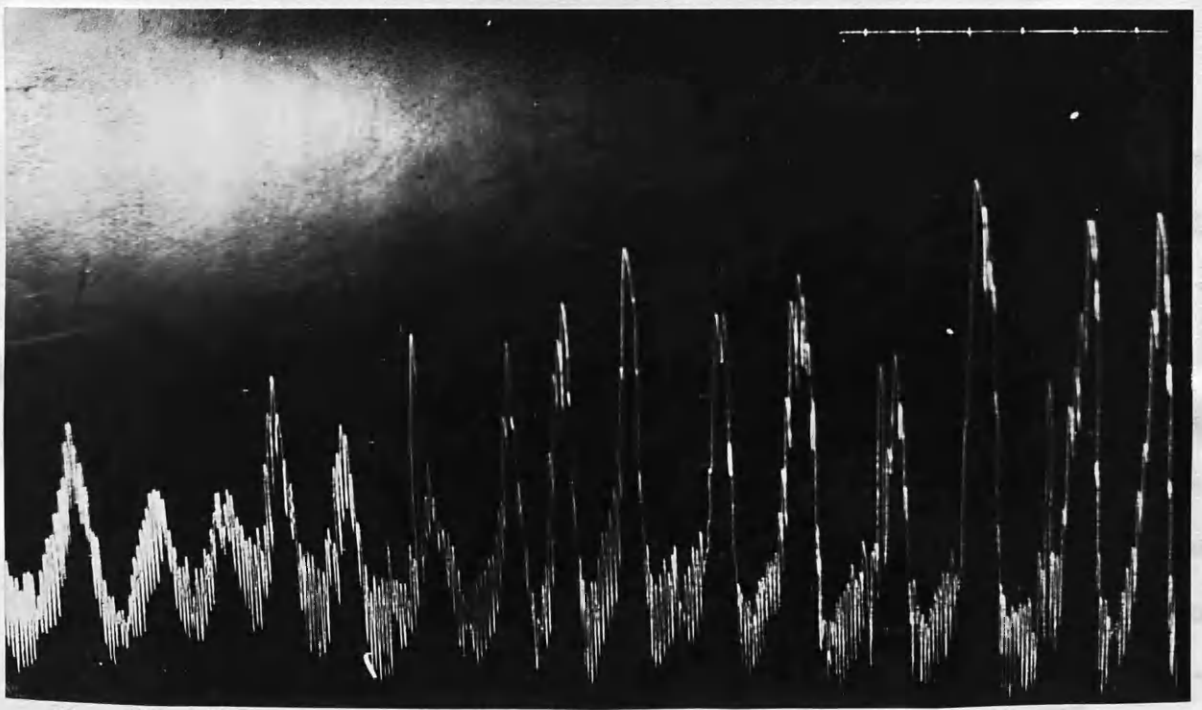
IV. Respiratory pressure rhythm.

My own findings are substantially the same; the activity of the fasting stomach has been divided into four phases:-

1. The Phase of Active Contractions:

These are identical with the hunger contractions described by Carlson, and are represented in the tracing by sharp-topped waves with a duration of thirty to forty seconds. (Figure 16).

Method A. Time Marker 30 secs.



Y. Y. Y. X. X. X.

Y. = High tonus waves changing into X.

X. = Hunger contractions.

Figure 16.

Carlson found that these contractions lasted from twenty to thirty seconds. These waves occur rhythmically in groups which last from a half to one hour. Between the individual contractions, short rest pauses occur lasting from ten seconds to five minutes. The number of contractions in a phase of activity is very variable, usually at least twenty are present. The frequency of the individual contractions also changes, but it is commonly in the region of fourteen contractions in twenty minutes.

2. The Tonus Wave:

Carlson described a tonus rhythm which was caused by contraction of the fundus. These contractions lasted on an average twenty seconds. The tonus wave noted in this investigation consists in a series of flat-topped waves of about ninety seconds in duration. These waves frequently precede true gastric contractions. When this change in the type of contraction occurs, one tonus wave follows more rapidly on another; the individual waves become shorter in duration and higher in amplitude, and thus merge into active fasting contractions. The occurrence of this tonus wave is not invariably followed by hunger contractions, as tonus rhythm may continue as long as two hours and then give place to a period of quiescence. This succession of tonus waves may also be seen after a period

of active contractions. No pause is present between the individual tonus waves, the one immediately following the other. (Figure 16).

In one case in which the balloon was lodged in the fundus, very typical flat tonus changes were seen. (Figure 14). The discrepancy between the tonus rhythm of Carlson and the tonus wave described here may be explained thus. In my own investigations, a larger balloon was used which, by more accurately filling the stomach, may have recorded a wave of greater duration. An extreme case is shown in the diagram. (Figure 17). In "B" every phase of activity of the fundus is recorded; in "A" activity begins only when tonus encroaches on that small portion of the fundus occupied by the balloon.

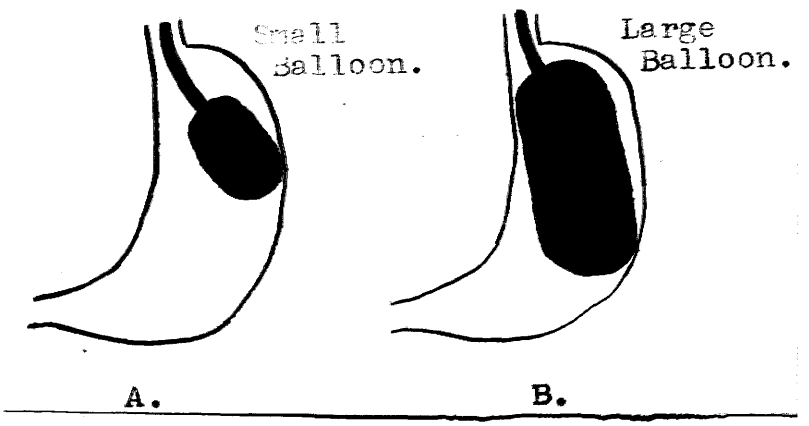


Figure 17.

3. A Phase of Relative Quiescence:

This term was used by Carlson to indicate the periods of rest which occur between the phases of contraction. I found that in what appeared to be a quiescent period, extremely flat-topped waves of about 2½ minutes' duration were occurring. These waves were of very low amplitude and represented slight but frequent changes in gastric tone. This phase is the nearest approach to complete rest found in the healthy fasting stomach. The occurrence of this wave is not described by other authors. (Figure 18).

Method A.

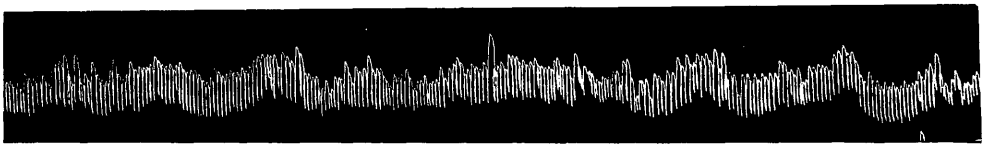


Figure 18.

4. A Tetanic Phase:

Carlson(1916) and Danielopolu(1930) observed this phase frequently. I have never seen it in the normal stomach. When a tetanic phase occurs, the active fasting contractions take place in quick succession until a phase of prolonged high intragastric pressure develops. It is said to be commoner in young and virile people, but this

has not been confirmed in the present investigation.

The onset of active fasting contractions is usually heralded by a gradual increase in amplitude of the tonus wave. The active fasting contractions may cease abruptly or may pass into the phase of tonus waves; but the most common type of cessation is an abrupt stop, and a subsequent period of relative quiescence. In the healthy subject, the gastric fasting contractions, once established, are usually regular in rhythm, of approximately equal amplitude and not super-imposed on each other.

S E C T I O N 6.

GASTRIC REFLEXES

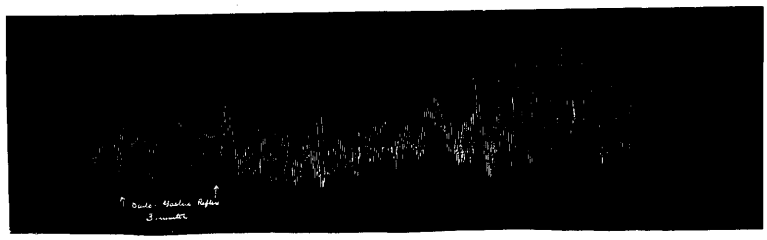
It has long been known that pressure on the eyeball or on the carotid sinus produces a slowing of the heart. Sachs (1936) records that Czermack in 1868, experimenting on himself, showed that pressure on the right vagus and on the carotid artery had the effect of slowing the pulse and the respirations.

A. Oculo-Gastric Reflex:

Danielopolu (1930) stated that moderate compression of the eyeball, insufficient to slow the pulse, had well defined effects on gastric motility. The phenomenon consists of a period of inhibition of gastric motility succeeded by a phase of excitation. (Figure 19).

The test was performed in three cases, and it was found necessary to compress both eyeballs with moderate force for at least two minutes in order to elicit the reflex.

Method A.



A. B. C.

Figure 19.

A. Both eyes pressed for three minutes.
B. Phase of inhibition.
C. Period of excitation.

The afferent fibres of the reflex travel probably in the trigeminal nerve. Discussing the oculocardiac reflex, Sachs(1936) quotes Barré and Crusem, who regard the ciliary nerves of the sclera as the afferent pathway. He also notes that Danielopolu and Guillaume conclude that the afferent fibres of the oculocardiac reflex run through both trigeminal and sympathetic nerves. It is thought that the efferent fibres of the oculo-gastric reflex run in the vagus, and the result of moderate pressure on the eye appears to be slight stimulation of the vagus. Cannon(1911) states that vagal activity may cause a preliminary lowering of tonus before the phase of increased movement is produced. According to Danielopolu(1930) both sympathetic and parasympathetic systems are involved. He holds that one and the same

stimulus may cause a sympathetic action on one organ and a parasympathetic effect on another. He concludes that the first inhibitory phase in this reflex may be due to sympathetic stimulation of the stomach, with parasympathetic stimulation of the heart, the parasympathetic effect on the stomach becoming manifest later. It is impossible to decide which of these theories is correct, but the view put forward by Danielopolu that the same stimulus may have a sympathetic effect on one organ and a parasympathetic effect on another will be found to be of considerable importance when the actions of calcium and other drugs are discussed.

B. Carotico-Gastric Reflex:

This reflex is obtained by compressing the right carotid bulb just below the angle of the lower jaw. The result is, (a) during the actual pressure, a slowing of gastric contractions followed by, (b) a state of hypermotility which eventually ends in (c) a phase of relative quiescence. (Figure 20).

Method A.

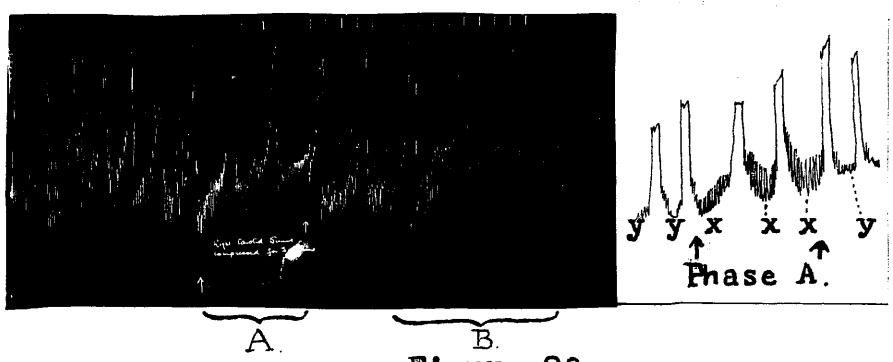


Figure 20.

A. Pressure on right Carotid Sinus accompanyied by a slowing of gastric contractions.

B. A state of hypermotility, which was followed by a phase of inhibition.

y = normal respiratory wave, x = increase in amplitude of this wave during carotid compression. (Phase "A").

The increased gastric motility was followed by a period of quiescence; and an increase in the amplitude of respiration was noted during pressure on the carotid (Phase "A"). Wright (1940) states that the external pressure on the carotid sinus stimulates the adventitial nerve-endings and reflexly slows the heart. If it is assumed that the efferent nerve for this reflex is the vagus nerve

then the action on the stomach may again be explained solely on the lines of Cannon's(1911) findings, namely, that vagal stimulation produces first a short inhibitory phase followed by a period of motor activity. The paralytic phase may be explained by exhaustion following hypermotility.

Danielopolu(1930) describes this reflex as a phase of hypermotility followed by a depressed phase. He adds that frequently a period of inhibition precedes hypermotility, usually during carotid compression. His published tracings invariably show an inhibitory phase. This worker's explanation of the reflex is that the inhibitory period depends on a momentary preponderance of the sympathetic system and the excitatory phase coincides with the control passing to the parasympathetic nerves. He attributes the paralysis to exhaustion.

It was found that to obtain these reflexes the stomach must be in a phase of active contractions. If the stomach was in a state of quiescence neither of these reflexes could be obtained. The importance of these reflexes lies in showing how extrinsic stimulation may alter the movements of the stomach.

SECTION 7.

PATHOLOGICAL CONDITIONS.

A priori it would appear that gastric motility should play an important part in the pathogenesis and symptomatology of lesions of the stomach and duodenum. It must be admitted, however, that marked changes from normal have not hitherto been described. Danielopolu(1930) stated that it was difficult to determine the limits of normality. However, he described as typical of gastric atony, a wave of small amplitude, and contractions which never proceeded to a tetanic phase. In six cases of pyloric stenosis he reported increased amplitude of contractions with marked irregularity and fusing of the waves. He also noted in this condition an arrhythmia, the waves varying in amplitude and duration. These phenomena, he added, were not pathognomonic of pyloric stenosis.

In the present investigation, an attempt has been made to determine whether any alteration in gastric motility can be distinguished as characteristic of pathological states of the stomach and duodenum. Among the conditions studied were (a) patients with gastro-enterostomy,

(b) patients with peptic ulceration, and (c) patients with gastric carcinoma.

(a) Patients with Gastro-enterostomy:

Observations were made on two patients.

Case I.

J.F., Male, aged 43. Bleeding piles. A gastro-enterostomy had been performed ten years previously.

Pain had recurred for the first time five months before admission, but on entering hospital it disappeared completely. When he was convalescent after surgical treatment for haemorrhoids, a gastrogram was made (Figure 21). It revealed that the phases of contractions were of the usual duration and the height of the wave and its shape were of practically normal appearance. The waves were strong and occasionally a slight fusing of contractions occurred.

Method A.

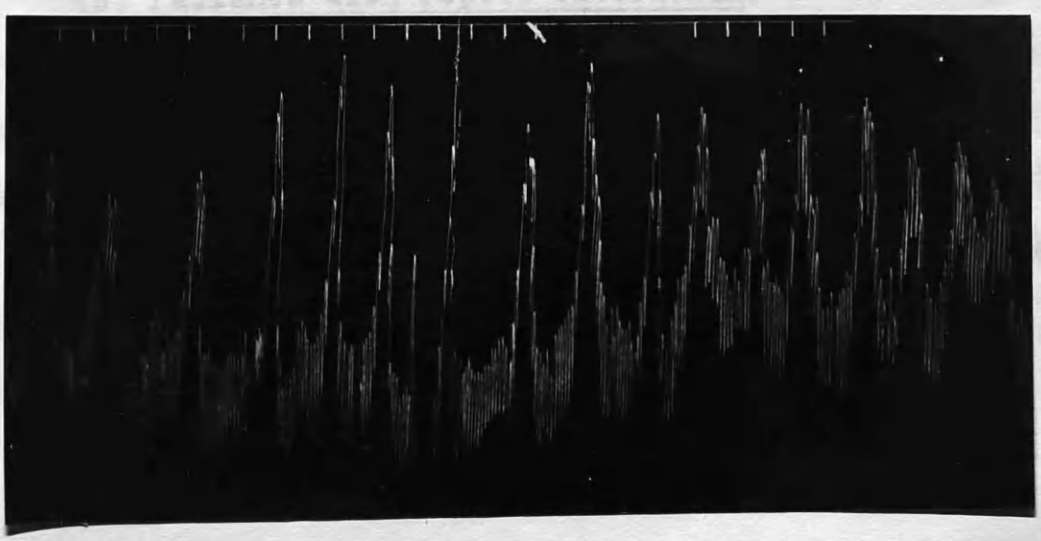


Figure 21.

Case II.

J.C., Male, aged 37. Recurring haematemesis. Gastro-enterostomy when 22 years of age.

Starting with a haematemesis six years ago, his symptoms have been consistent with peptic ulceration. After five weeks of medical treatment a gastrogram was obtained. The contraction waves had a large amplitude, varied slightly in height and were practically regular in rhythm. No fusing of waves was seen and no abnormality was observed.

From these two cases, it may be concluded that normal contractions occur in patients who have had a gastro-enterostomy performed. This conforms with Cannon's views for in 1911 this worker stated that there was no reason for thinking that peristalsis ceased after gastro-enterostomy or that the food was not thoroughly churned in the pyloric end in the normal manner.

(b) Patients with Peptic Ulceration:

Dundon(1917) produced ulcers in the stomach and duodenum of dogs, and found in three quarters of the dogs greater motility than in the normal empty stomach.

Onodera, Kanegae, Matufuzi and Hasi,(1931) as a result of an investigation in one thousand different patients, described three types of ulcer.

(1) When a relatively acute ulcer is present, the gastric tone is increased and the contractions are deeper and quicker than normal.

(2) With slight pyloric stenosis associated with peptic ulceration, the tone is decreased and contractions are irregular with longer periods of quiescence.

(3) With advanced pyloric stenosis and dilatation of the stomach, there is a marked reduction in tone and hunger contractions are weak.

Danielopolu[1930] stated that in gastric ulcers the inflation of the balloon caused pain and that strong tetanic contractions sometimes occurred. Brauch[1937] studied sixty-four patients with peptic ulcer by the balloon method, and came to the conclusion that the important findings were irregular peristalsis, increased irritability of the stomach and a tendency to hyperperistalsis. He applied the term "gastric arrhythmia" to the disorganised peristaltic movements which were occasionally observed. This author was unable to divide his cases into the different categories enumerated by Onodera and his co-workers.

During the present study twelve patients with various clinical types of peptic ulcer were examined.

Case I.

Acute Duodenal Ulcer. J.D., Male, 22 years:

Epigastric pain of three years' duration related to food and relieved by alkali. Remissions last three to four months. Epigastric tenderness present. Blood in gastric juice. Faecal occult blood test positive. Diagnosis of duodenal ulcer confirmed radiographically.

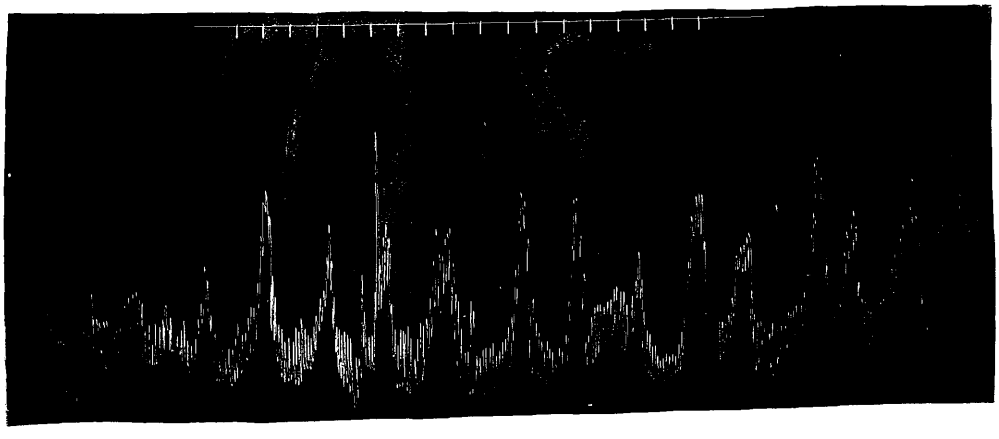
Gastrogram: Powerful fasting contractions varying in amplitude. Fusion of waves was noted. The patient complained of his usual stomach pain and this was found to be present only when a contraction occurred.

Case II.

Acute Duodenal Ulcer. W.M., Male, 19 years:

Intermittent epigastric pain of two years' duration. The most recent attack occurred six months prior to admission and in this the pain was most severe just before the next meal was due. Epigastric tenderness present. X-ray examination revealed the presence of a duodenal ulcer.

(a) Method A.



(b) Method A.

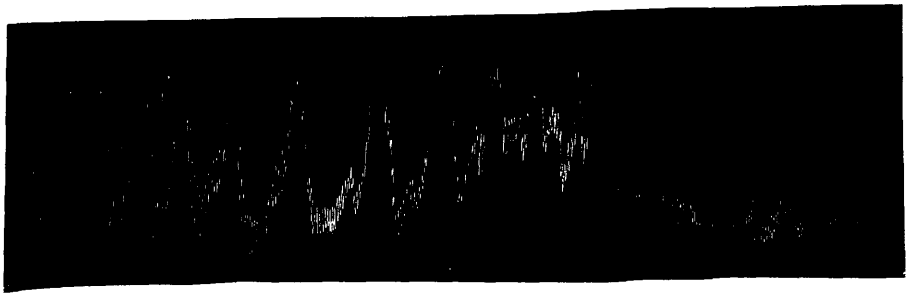


Figure 22.

Gastrogram (Figure 22 (a) and (b): The contraction waves were irregularly irregular in rhythm and of high amplitude. They tended to fuse and to become superimposed on each other. Frequently a tetanic phase developed. Pain was present when strong contractions occurred. This pain was similar to that which commonly occurred just before the patient's next meal.

Case III.

Acute Duodenal Ulcer. B.W., Female, 25 years:

Epigastric pain of two years' duration. Remission periods of two to three months have occurred. Pain commenced after food, occasionally before meals, and was relieved by alkali. Epigastric tenderness present. Radiographic evidence of a duodenal ulcer was found.

Method A.

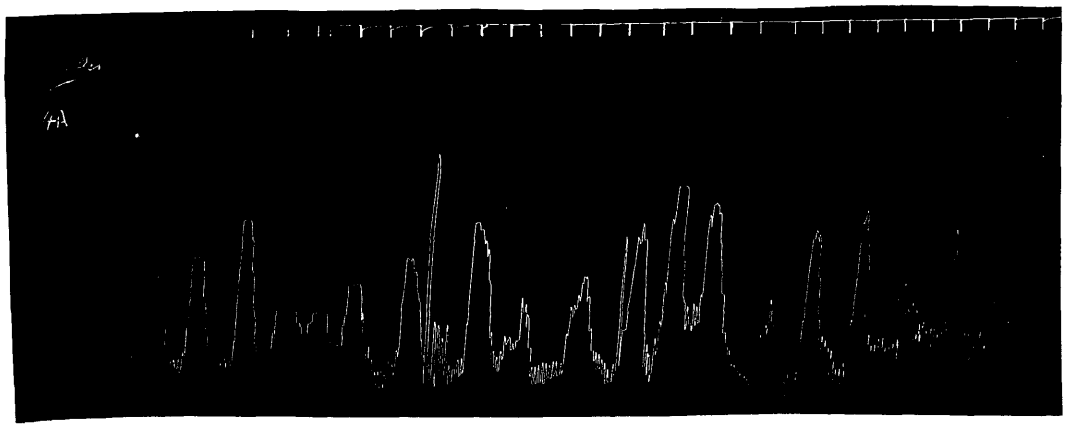


Figure 23.

Gastrogram (Figure 23): The fasting contractions were powerful in amplitude, irregularly irregular in rhythm. Fusing of the waves occurred and periods of

tetanus were present. No pain was present when the recording was taking place.

Case IV.

Acute Duodenal Ulcer. D.M., Male, 57 years:

Intermittent epigastric pain and loss of weight of one year's duration. Present attack started four weeks' ago with discomfort after food relieved by alkali or by vomiting. Blood in gastric juice. X-ray examination confirmed the presence of a duodenal ulcer.

Gastrogram. Strong contractions regular in rhythm but varying markedly in amplitude. No pain was present during the period of examination.

Case V.

Acute Duodenal Ulcer. J.H., Male, 26 years:

Haematemesis two years ago followed by intermittent epigastric pain which appeared after food and was relieved by alkali. Recent loss of weight. Ulceration of duodenum confirmed radiographically.

Gastrogram. Variation in the amplitude of the contraction wave; some waves were powerful, others weak. The rhythm was irregularly irregular. While the balloon was in situ, no pain was felt by the patient.

Case VI.

Recurrent Duodenal Ulcer. A.A., Male, 36 years:

Intermittent epigastric pain of eight years' duration with periods of freedom from discomfort lasting sometimes six months. Pain, more acute in the week prior to admission, was relieved by vomiting. Tenderness present in epigastrium. X-ray examination showed a deformed duodenal cap with a recurrence of duodenal ulceration.

Method B.

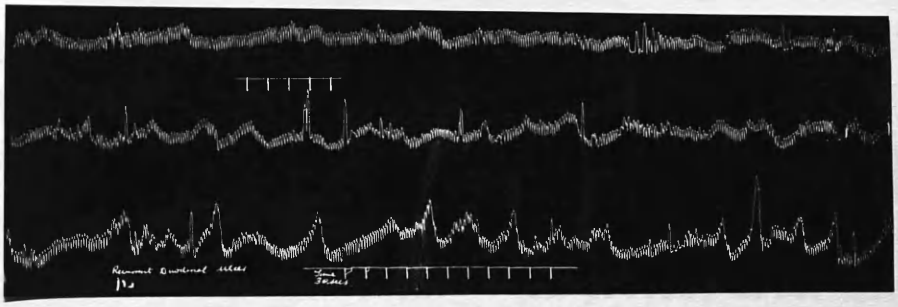


Figure 24.

Gastrogram (Figure 24). The contractions were of moderate strength and irregular in rhythm, showing some fusing.

Case VII.

Recurrent Duodenal Ulcer. R.S., Male, 22 years:

Epigastric pain coming on two hours after food of three weeks' duration accompanied by loss of weight. Tenderness present in epigastrium. Faecal occult blood test positive. X-ray examination showed a deformed tender duodenal cap.

Method B.

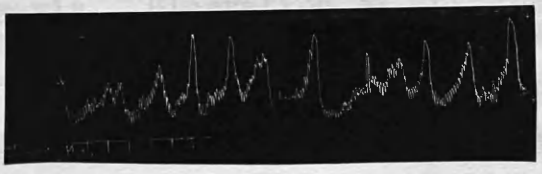


Figure 25.

Gastrogram (Figure 25). The fasting contractions were powerful, regular in rhythm and fusing, one occurring on top of the other. They showed a great variation in amplitude; no pain was felt during the time of

observation.

Case VIII.

Recurrent Duodenal Ulcer. D.C., Male, 36 years:

Pain in upper part of the abdomen of three years' duration. At that time the presence of a duodenal ulcer was confirmed radiographically. Since then several relapses have occurred, the most recent starting five weeks prior to admission. Pain present after meals relieved by the taking of food. Epigastric tenderness with slight rigidity. Faecal occult blood test positive. Duodenal ulceration confirmed by X-ray.

Gastrogram. Irregular irregularity in rhythm and force. No other abnormality was noted in the tracings and no pain was felt by the patient at any time during the investigation.

Case IX.

Recurrent Duodenal Ulcer. E.L., Male, 47 years:

Intermittent epigastric pain of fifteen years' duration with periods lasting for six months of freedom from discomfort. Pain occurring after meals relieved by alkali, vomiting and the taking of food. Epigastric tenderness present. Faecal occult blood test positive. Hyperchlorhydria. Ulceration of duodenum with cicatrisation from old duodenal inflammation found on X-ray examination.

Gastrogram. The fasting contractions showed no abnormality beyond an irregular irregularity in rhythm. No pain was felt by the patient during the time of observation.

Case X.

Chronic Duodenal Ulcer. J.J., Male, 32 years:

Epigastric pain of four years' duration with remissions lasting four months. Discomfort coming on after meals relieved by food and by MacLean's powders. Tenderness present in mid-epigastric region. Persistent irregularity of duodenal cap with associated tenderness found on X-ray examination.

Gastrogram. The fasting contractions showed no abnormality beyond slight fusing of the individual waves. The patient made no complaint of pain during the investigation.

Case XI.

Acute Gastric Ulcer. J.L., Male, 20 years:

Epigastric pain after food of nine years' duration. Appendicectomy six years ago. Vomiting since then has occurred periodically. Epigastric tenderness. Faecal occult blood test positive. Hyperchlorhydria. Prepyloric ulcer with localised pyloric spasm seen on X-ray examination.

Method A.

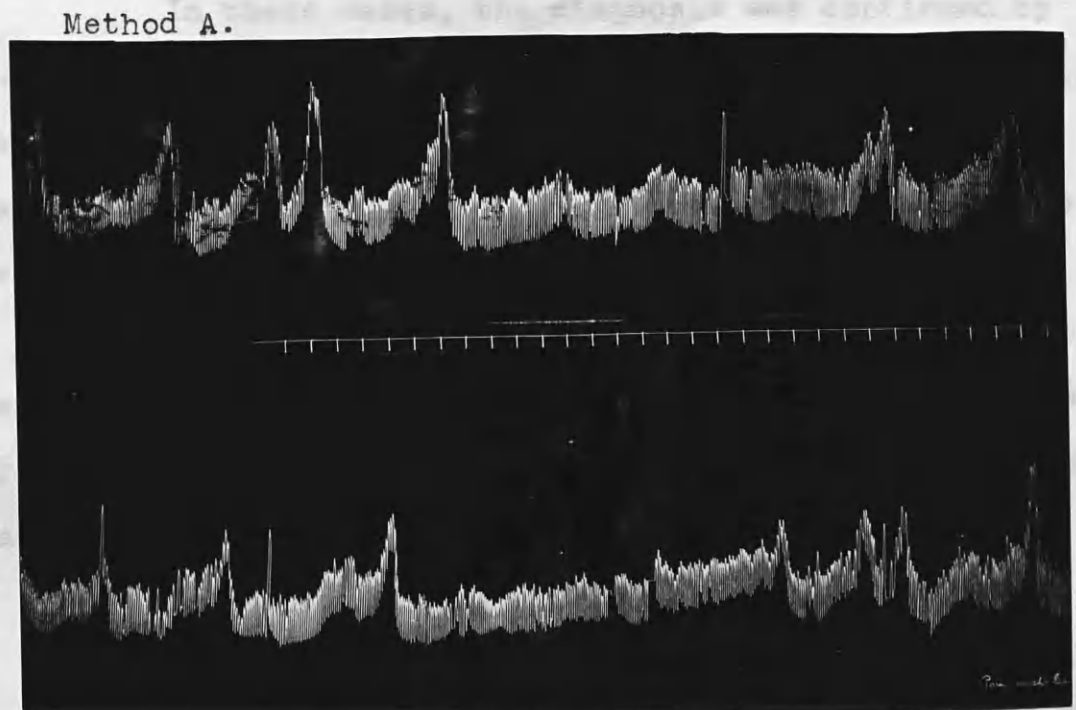


Figure 26.

Gastrogram (Figure 26). The tracing showed infrequent contractions of low amplitude, irregular in rhythm and tending to fuse. The patient complained of pain when no contraction was seen on the tracing, while during contractions no pain was felt. The pain was not relieved by atropine gr.1/100 given subcutaneously.

Case XII.

Chronic Gastric Ulcer. C.D., Male, 53 years:

Intermittent abdominal pain after food of twenty-two years' duration. Remissions lasting six months have occurred. No tenderness. Faecal occult blood test positive. Presence of gastric ulcer confirmed by X-ray examination.

Gastrogram. Powerful gastric contractions were present which tended to fuse. Contractions were regular and the patient made no complaint of pain while under observation.

In these cases, the diagnosis was confirmed by x-ray examination. In all the acute cases, pain was still occurring intermittently, but in the chronic relapsing cases, pain had been absent for some time, although radiographic evidence of ulcer was still present.

The records show that the movements seen in the fasting stomach of a patient with peptic ulcer often closely resemble the normal hunger contractions. Usually slight fusing of the waves is seen in such cases, but this has

also been found in normal people; and, as shown in the previous section, fusing may also occur in the healthy subject with a gastro-enterostomy.

In the presence of acute duodenal ulcers the contractions resemble closely those described by Onodera and his colleagues(1931) as a Type I. ulcer curve, i.e. the gastric tone is increased and the contractions are deeper and quicker than normal. These tracings frequently end in tetanic spasms. In patients with duodenal ulcers, powerful contractions were found in six out of ten cases, and the arrhythmia gastrica of Brauch in a like number. It would appear therefore that powerful gastric contractions, irregular in rhythm and with a tendency to fuse, favour a diagnosis of duodenal ulcer.

In the acute gastric ulcer case, on the other hand, the contractions were weak and of small amplitude but with the same tendency to fuse as in patients with duodenal ulcers. The periods of fasting gastric contractions were infrequent, but once started they lasted longer than usual and there were longer intervals between the contractions. These findings resemble closely the description given by Onodera for his Type II. curve.

In a case of chronic gastric ulcer, the contractions were powerful and tended to fuse. Although there is a characteristic type of tracing for each form

of peptic ulcer, it must be noted that apparently normal contractions may be found, particularly when the ulcer is in the duodenum. In other words, it would be impossible to diagnose the condition of the stomach or duodenum from the character of the fasting contractions alone. Typical findings would serve, however, to strengthen a presumptive diagnosis of ulceration.

(c) Patients with Gastric Carcinoma:

Onodera, Kanegae, Matufuzi and Hasi (1931) showed that in cases of gastric carcinoma the gastrogram was always abnormal; the fasting contractions were slow, few in number and never culminated in a tetanic phase. Two cases are described here with a third probable case of carcinoma.

Case I.

T.M., Male, aged 58 years, had had pain in stomach of nine months' duration. At that time, the patient vomited blood and had discomfort in the upper part of the stomach. This pain was not severe but of constant character, unaffected by the taking of food. Two months later, another haematemesis occurred. Laparotomy was performed revealing a carcinomatous tumour in fundal part of stomach. The presence of an irregular mass about two inches below the costal margin was found on abdominal examination.

Method B. s s

s = Sigh.

Figure 27

Gastrogram (Figure 27). A single series of eight fasting contractions was observed. They were of low amplitude, of normal duration and were regular in rhythm. Fusing of the contractions was seen.

Case II.

P.B., Male, aged 61 years, admitted with a complaint of burning pain in the stomach after food, of four weeks' duration, accompanied by a loss of weight. Vomiting has troubled the patient on several occasions. Epigastric tenderness was found. Test-meal revealed a normal acidity with the presence of blood throughout, and x-ray examination showed a large penetrating gastric ulcer on the lesser curvature. The appearance of this suggested that it was malignant.

Method B.

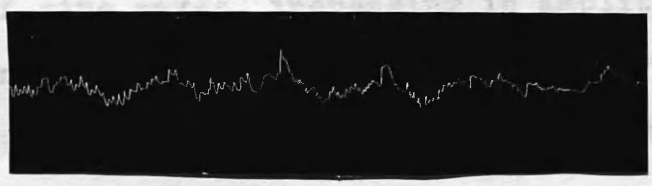


Figure 28.

Gastrogram (Figure 28). The period of contractions observed was very short consisting of five waves of regular rhythm, low amplitude, and each lasted at least 35 seconds. No phase of regular tonus rhythm was seen.

The next case investigated was that of a patient with a large gastric ulcer situated on the lesser curvature of the stomach and probably undergoing malignant change.

J.G., Male, aged 44 years, had had pain in stomach after meals of six weeks' duration. This pain was relieved by alkaline powders and food. Tenderness was present in the epigastrium and a test-meal showed a low normal acidity. The first x-ray revealed a large gastric ulcer; the second, one month later, showed no change in the condition and the radiologist suggested that it was malignant. The patient refused operation and was dismissed against medical advice.

Method B.

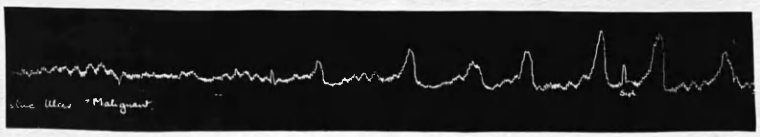


Figure 29.

Gastrogram (Figure 29). The phase of contractions consisted of nine waves, increasing in amplitude, regular in rhythm and lasting thirty-five seconds. Fusing of waves was not seen but slight variation in amplitude of the individual waves was noted.

My observations enable me to confirm the findings of Onodera et alii that carcinoma of the stomach reduces the number of fasting contractions. This was a striking feature in all three cases. The contractions in the first two cases were of low amplitude. The duration of each wave and the period between the individual contractions were within normal limits. Thus apart from the small number of contractions, there was nothing in

the tracing characteristic of gastric carcinoma. In Cases I. and II., the waves were of much lower amplitude than those seen normally, but in Case III. the waves were of normal appearance - though fewer in number.

S E C T I O N 8.

A NOTE ON PAIN IN PEPTIC ULCERATION

The hypotheses suggested as an explanation of pain in peptic ulceration may be divided, as Granet (1933) suggests, into three groups:-

1. Increased muscle tension.
2. Chemical irritation of the ulcer.
3. Kinsella's Compression Theory.

1. Increased Muscle Tension:

Abnormally deep muscular contractions in the form of strong hunger or fasting movements were first suggested by Ginsburgh, Tumpowsky and Hamburger, (1916) as being closely connected with the pains of peptic ulceration. Carlson (1917) was also able to correlate the occurrence of the hunger contraction and the onset of the pain. He noted that the fasting movements which caused pain in the ulcer patient were not stronger than usual, and so postulated an increased sensitivity of the nerve endings in such cases. He explained that a contraction which would not cause pain in the normal healthy individual would, however, excite it in the ulcer patient, due to this increased sensitivity. Hardt (1918) stated

that the pain was intermittent, being synchronous with the contractions of the stomach, pylorus or duodenum. Ortmayer(1925) could not satisfy herself of a relationship between the hunger contractions and the pain. She found that while the administration of alkali relieved the pain, the peristaltic movements of the stomach remained unaltered. Christensen(1930) and Smith, Paul and Fowler(1930) supported the hunger contraction theory. Smith and his co-workers held this view because they found that ulcer distress could be relieved by the intravenous injection of atropine, grain 1/50th.

Dimitriu, Tanasoca and Popovici(1938) found that when pain occurred in gastric ulcer, contractions of the stomach were always present. Hurst(1929) concluded a detailed discussion by stating that the pain of duodenal ulcer, as distinct from the pain of gastric ulcer, depended upon an increase of muscle tension which developed in some way when a small quantity of acid contents was present in the stomach. He further maintained that this increase in tension occurred in the pyloric vestibule and was due to spasm of the pyloric sphincter accompanied by deep peristaltic waves which, by the time they reached the vestibule, almost completely separated its contents from those of the proximal portion of the stomach. Consequently, the pressure in the small distal segment rose unless the

pyloric sphincter at the same time relaxed; if, for any reason, the sphincter did not relax there was a marked rise of pressure. This produced an abnormal increase of tension in the individual fibres of the muscular coat of the pyloric vestibule and resulted in pain. Hurst attributed the pain in gastric ulcer to an increase in pressure in the proximal portion of the stomach, the obstruction at the site of the ulcer being due in this instance to a spasmodic hour glass constriction. Glaessner and Kreuzfuchs (1913) thought that spasm of the pylorus and the duodenal cap was the most important factor in the causation of pain in peptic ulcer. Changes in the tonus of the duodenum have been shown by Ivy, Vloedman and Keane (1925) to occur with a rhythm similar to the tonus change of the stomach and to take place almost synchronously. They suggested that the hunger pains were related more closely to the contractions of the duodenum than to those of the stomach. Wilson (1928) supported this view, finding by x-ray examination that the gastric waves were not connected with the pain of duodenal ulcer. He thought that the pain was due to a sustained contraction of the duodenum.

2. Chemical Irritation of the Ulcer:

Talma in 1884 reported the production of severe epigastric distress by the injection of 500 c.c. of a

solution of hydrochloric acid (1:750) into the stomachs of two patients, one with a gastric carcinoma and the other with a benign peptic ulcer. This was confirmed by Suyling in 1888, and Bönninger in 1909 found that the distress of gastric ulcer could be brought on regularly when a decinormal solution of hydrochloric acid was introduced into the stomach. In 1912, Sippy stated that the pain and discomfort of uncomplicated ulcer was due to the irritative action of the hydrochloric acid on the nerves exposed in the ulcer. Palmer(1926b) found that the pain in patients with peptic ulcers could be produced by introducing into the stomach hydrochloric acid in strength varying from 0.2 to 0.5 per cent. Palmer and Heinz(1934) gave a very complete review of the literature and concluded that ulcer pain was not directly connected with pylorospasm, gastric motility or intra-gastric pressure, but depended on the presence of an adequate stimulus acting on an irritable pain-producing mechanism located in or adjacent to the lesion itself. This adequate stimulus might be - (a) mechanical, due to peristaltic traction or local spasm, or (b) chemical, due to the acid reaction of the chyme. The usual stimulus, however, was said to be the free hydrochloric acid of the gastric contents and the action was probably exerted directly on nerves rendered excessively irritable by inflammation resulting from the

destructive effect of the acid gastric juice.

In contra-distinction to the work previously described, Lowenthal,(1892) Schmidt,(1909) Boring,(1915) Hurst,(1911) and Reynolds and McClure(1922) had introduced varying amounts of hydrochloric acid into the empty stomach in concentration of from 0.5% to 2% without producing distress in either normal persons, or in patients with ulcer. Hardt(1918) found that ulcer pains might be present when aspiration of the contents of the stomach revealed no free hydrochloric acid and that these pains might be relieved by the addition of 0.3% hydrochloric acid to the stomach. He also pointed out that gastric ulcer pains may be absent in the presence of high acidity. He concluded that any active process (ulcer or carcinoma), producing an abnormally irritable condition, might cause intermittent pain synchronising with the contractions of the stomach, pylorus or duodenum, but bearing no relation to the degree of acidity. Christensen,(1931) also, found no relation between the spontaneous variations in the acidity of the stomach content and the appearance or the intensity of the pain.

It is interesting to note that Meyer, Fetler and Strauss(1932) concluded from their investigations on the relation of ulcer pain to gastric motility and acidity that the patients were found to fall into two classes:-

(1) those who had pain response to an acid stimulus but showed no pain in relation to gastric motility, and (2) those who had no pain following an acid stimulus but had pain during periods of gastric motility.

3. Kinsella's Compression Theory:

Kinsella (1928, 1929, 1940) put forward the view that pain was caused by compression of sensitized sensory nerves in and around the ulcer base produced by - (1) inflammatory oedema, (2) increased muscle tone or spasm, and (3) localised vascular engorgement. These three phenomena occurred in and around the ulcer crater. He stated that the relief of ulcer pain depended on a decrease in tissue tension. According to Alvarez, (1940) Ivy supported a similar hypothesis for the continuous type of distress met with in ulcer pain. He believed that the intermittent type of ulcer pain was probably due to changes in tonicity of the muscle at the site of the ulcer, brought about by peristalsis or local spasm.

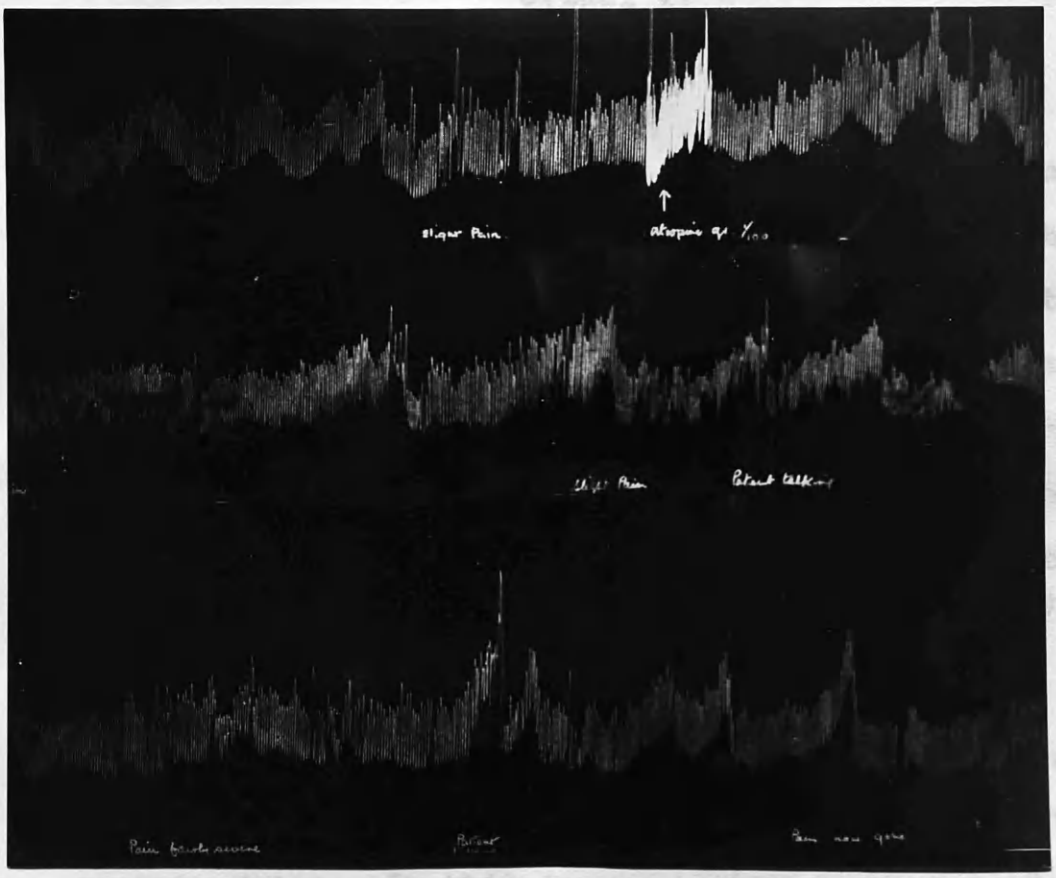
Among my own patients pain occurred in three of the ulcer cases while under observation. In one patient with a duodenal ulcer, the pain was present on numerous occasions. The two patients with acute duodenal ulceration, complained of pain which coincided with the appearance of a gastric contraction on the tracing. In these

cases, the pain was of spasmodic type. The contractions which occurred when the pain was present were strong and on one occasion tetanic in character. This tetanic phase was accompanied by severe pain. In these two cases, the pain appeared to be related to contraction of the stomach.

In the acute gastric ulcer case in which pain was present, the pain was more constant in character and of a gnawing type. When it occurred, there was usually no evidence of gastric contractions. In this particular patient, gastric contractions were found to occur without accompanying pain. (Figures 30, 31).

Method A.

X.

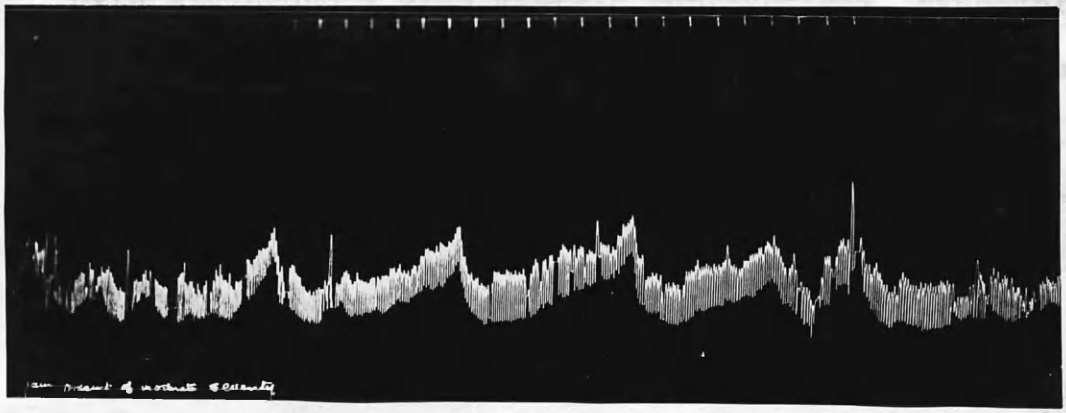


Y. Z.

Figure 30.

At X. and Y. pain is present but no contraction.
At Z. a gastric contraction is present without the occurrence of pain.

Method A.



X.

At X. pain present without the occurrence of a contraction.

Figure 31.

In the patients with duodenal ulcer, the contractions of the stomach which were powerful and in one case tetanic, may have caused the pain. On the other hand, it has been shown that very powerful contractions occurred in the stomachs of normal subjects without causing pain. The relation of gastric contraction to the onset of the pain is difficult to explain but may be due to duodenal contraction occurring synchronously with the gastric contraction. Ivy, Vloedman and Keane (1925) suggest that this does occur.

It is, of course, possible that in duodenal ulceration, the pain is brought on by the action of the gastric juice. In this investigation three out of ten cases of duodenal ulcer showed a hyperchlorhydria, the

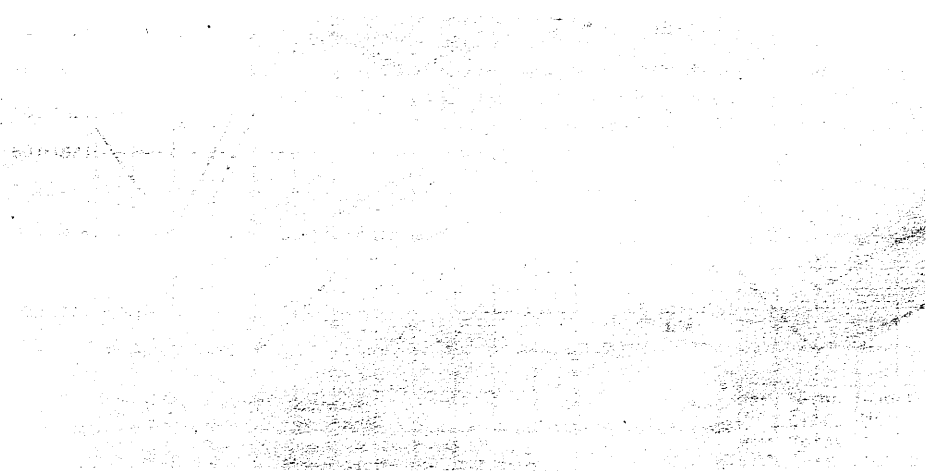
rest a normal acidity, while of the two cases which had pain synchronous with gastric contractions, hyperchlorhydria was found in one case, a normal acidity in the other. It is concluded that in duodenal ulceration, while the effect of the hydrochloric acid as a pain-producing stimulus cannot be ignored, gastric contractions appear to be much more important.

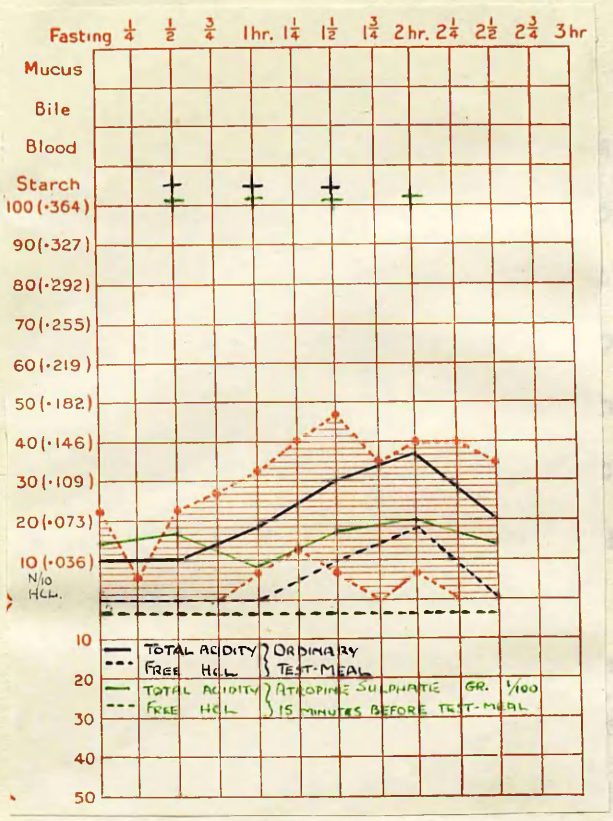
Of interest in this connection is the clinical finding that the administration of large doses of atropine is valuable in patients with duodenal ulceration, when the ulcer pain proves resistant to dietetic treatment.

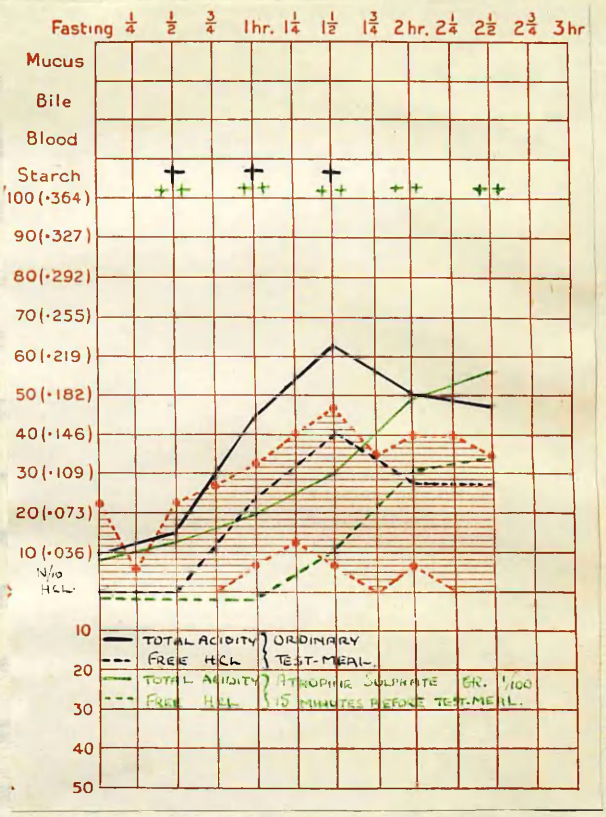
In one patient, (Case I. p.46) with an acute duodenal ulcer, who was treated with Sippy's regime and who, on three occasions, could not tolerate any increase beyond the first week's diet, which had now been given for three weeks, the administration of atropine was apparently beneficial. Atropine sulphate gr.1/50 was given hypodermically at 10 a.m. and 8 p.m. for seven days. The patient, who had previously complained bitterly of pain after food, and during the night, felt much better. Nocturnal pain disappeared, and he was able to take the second week of the Sippy diet, without recurrence of pain. He had no further trouble and made a quick recovery. Notwithstanding the large doses of atropine there were no complaints of dry mouth, thirst or difficulty in reading.

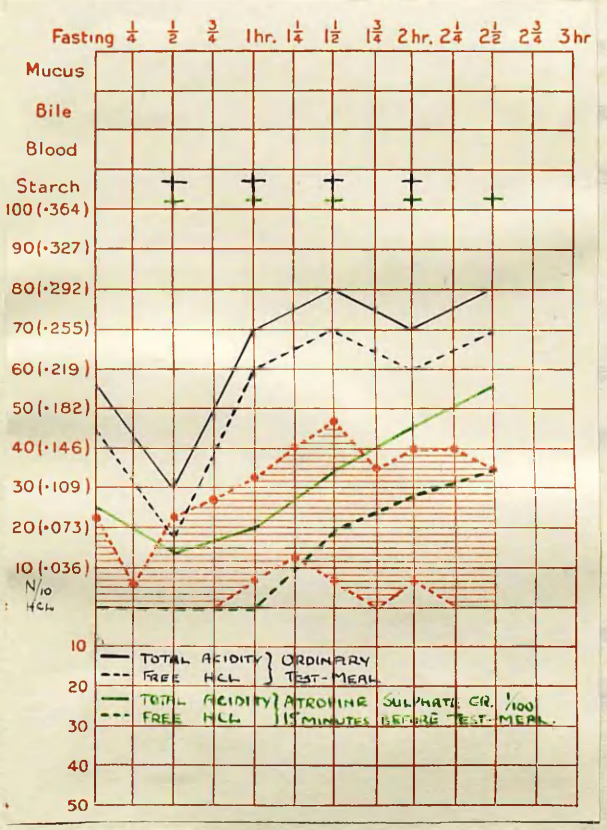
Ulcer patients who do not respond to milk diet and alkali are not common, but in two ulcer cases of this type, atropine in single doses of 1/50th grain has been used with apparent success, after the pain had persisted throughout a period of diet of the lightest possible kind.

In drawing deductions from these successful results with atropine in the control of duodenal ulcer pain, the effect of the drug on gastric secretion as well as muscle spasm, must be remembered. Controlled observations by Bennett (1923) and others have shown that the administration of atropine sulphate before a test-meal, causes a reduction in the height of the acid curve. Test-meals with atropine premedication are shown here. (Figure 32).




Fasting ¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr
Mucus
Bile
Blood
Starch
100 (·364)
90 (·327)
80 (·292)
70 (·255)
60 (·219)
50 (·182)
40 (·146)
30 (·109)
20 (·073)
10 (·036)
N/10 HCL
10
20
30
40
50
TOTAL ACIDITY } ORDINARY
FREE HCL } TEST-MEAL
TOTAL ACIDITY } ATROPINE SULPHATE GR. 1/100
FREE HCL } 15 MINUTES BEFORE TEST-MEAL


Fasting ¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr
Mucus
Bile
Blood
Starch
100 (·364)
90 (·327)
80 (·292)
70 (·255)
60 (·219)
50 (·182)
40 (·146)
30 (·109)
20 (·073)
10 (·036)
N/10 HCL
10
20
30
40
50
TOTAL ACIDITY } ORDINARY
FREE HCL } TEST-MEAL.
TOTAL ACIDITY } ATROPINE SULPHATE GR. 1/100
FREE HCL } 15 MINUTES BEFORE TEST-MEAL.


Fasting ¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr
Mucus
Bile
Blood
Starch
100 (·364)
90 (·327)
80 (·292)
70 (·255)
60 (·219)
50 (·182)
40 (·146)
30 (·109)
20 (·073)
10 (·036)
N/10 HCL
10
20
30
40
50
TOTAL ACIDITY } ORDINARY
FREE HCL } TEST-MEAL
TOTAL ACIDITY } ATROPINE SULPHATE GR. 1/100
FREE HCL } 15 MINUTES BEFORE TEST-MEAL.

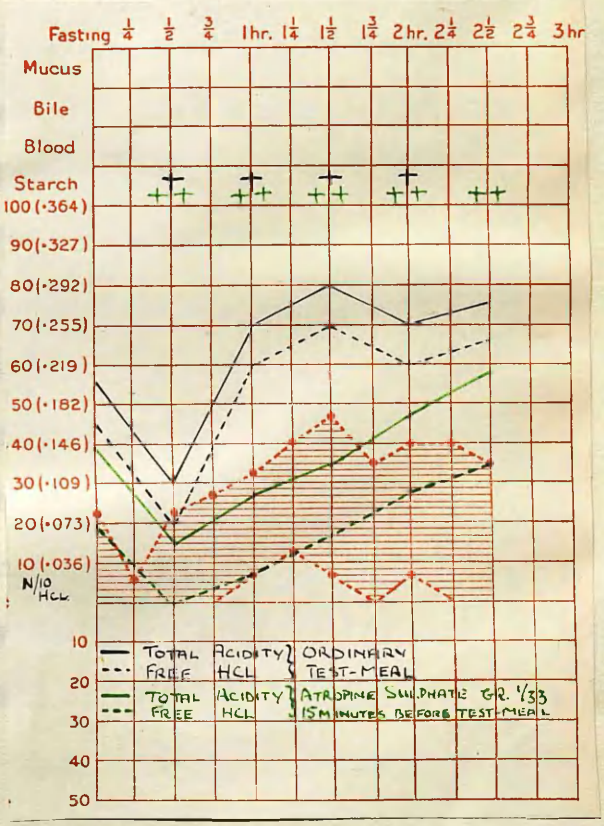
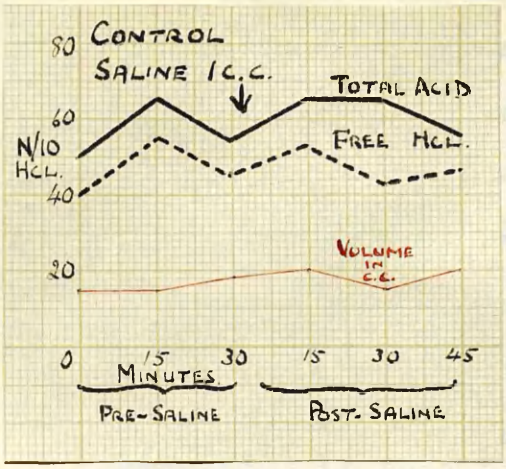

Fasting ¼ ½ ¾ 1hr. 1¼ 1½ 1¾ 2hr. 2¼ 2½ 2¾ 3hr
Mucus
Bile
Blood
Starch
100 (·364)
90 (·327)
80 (·292)
70 (·255)
60 (·219)
50 (·182)
40 (·146)
30 (·109)
20 (·073)
10 (·036)
N/10 HCL
10
20
30
40
50
TOTAL ACIDITY } ORDINARY
FREE HCL } TEST-MEAL
TOTAL ACIDITY } ATROPINE SULPHATE GR. 1/33
FREE HCL } 15 MINUTES BEFORE TEST-MEAL

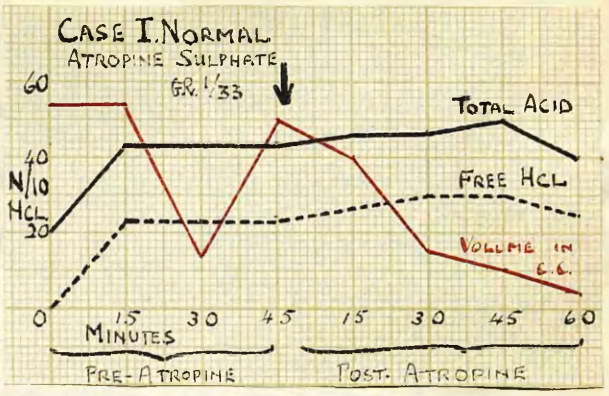
Figure 32.

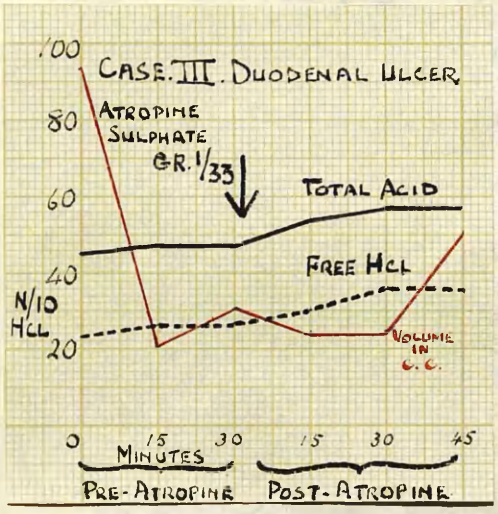
It will be noted that in addition to a reduction in the height of the free acid curve there is a marked delay in the emptying time following the atropine administration. It is possible, therefore, that the soothing effect of atropine on the pain which occurs after meals in peptic ulceration is due in part, if not entirely, to the reduction of gastric acidity. In duodenal ulceration, however, pain is not an infrequent symptom at night, when the stomach is empty. In view of this the effect of atropine on the fasting juice was determined.

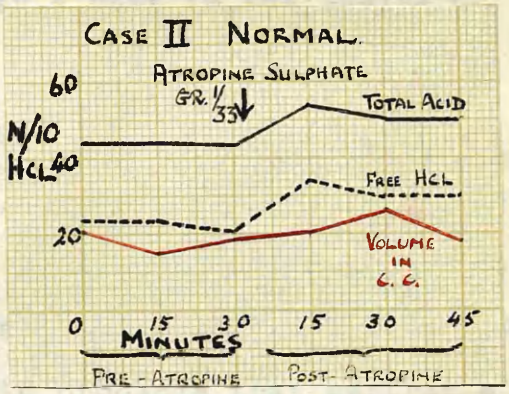
The action of atropine gr.1/33 was studied in the fasting juice in two normal subjects, in three patients with peptic ulceration, and in one with achlorhydria. The patient had received no food for twelve hours; a Ryle's tube was passed and an attempt was made to aspirate the stomach contents completely by removing as much juice as possible. The aspiration was repeated after a quarter of an hour and after half an hour. Then atropine sulphate gr.1/33 was given subcutaneously. After fifteen minutes the stomach was again emptied. This was repeated twice at fifteen minute intervals. No gruel was given throughout the procedure.

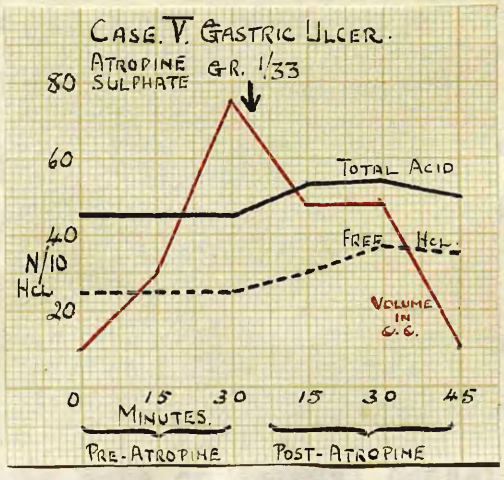
The effect of the atropine on the volume of secretion and on gastric acidity was then estimated. (Figure 33).

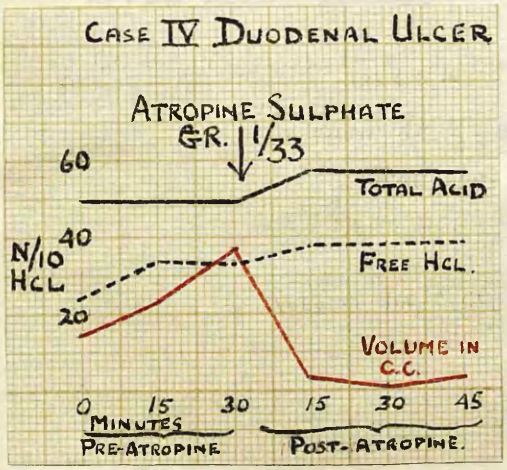

CONTROL
SALINE 1 C.C.
TOTAL ACID
FREE HCL.
N/10 HCL.
VOLUME IN C.C.
MINUTES
PRE-SALINE
POST-SALINE


CASE I. NORMAL
ATROPINE SULPHATE GR. 1/33
TOTAL ACID
FREE HCL
N/10 HCL
VOLUME IN C.C.
MINUTES
PRE-ATROPINE
POST-ATROPINE


CASE III. DUODENAL ULCER
ATROPINE SULPHATE GR. 1/33
TOTAL ACID
FREE HCL
N/10 HCL
VOLUME IN C.C.
MINUTES
PRE-ATROPINE
POST-ATROPINE


CASE II NORMAL.
ATROPINE SULPHATE GR. 1/33
TOTAL ACID
FREE HCL
N/10 HCL
VOLUME IN C.C.
MINUTES
PRE-ATROPINE
POST-ATROPINE


CASE V. GASTRIC ULCER.
ATROPINE SULPHATE GR. 1/33
TOTAL ACID
FREE HCL
N/10 HCL
VOLUME IN C.C.
MINUTES
PRE-ATROPINE
POST-ATROPINE


CASE IV DUODENAL ULCER
ATROPINE SULPHATE GR. 1/33
TOTAL ACID
FREE HCL.
N/10 HCL
VOLUME IN C.C.
MINUTES
PRE-ATROPINE
POST-ATROPINE.

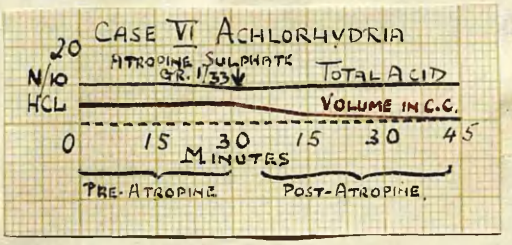

CASE VI ACHLORHYDRIA
ATROPINE SULPHATE GR. 1/33
TOTAL ACID
VOLUME IN C.C.
N/10 HCL
MINUTES
PRE-ATROPINE
POST-ATROPINE.

Figure 33.

In four cases there was a reduction in the volume of fasting juice following the atropine, but in the others the volume did not diminish. No significant alteration could be detected in the concentration of free acid. These results suggest that with adequate dosage the volume of the acid gastric secretion may be significantly reduced and that this may play a part in the easing of pain in peptic ulceration.

On page 53, observations were described on a patient with a gastric ulcer, who was suffering from pain at the time of examination. As in gastric ulcer cases, no relationship has been established between contractions of the stomach and pain, it is probable that gastric acidity was mainly responsible in this case, for there was marked hyperchlorhydria. Bell(1923) however, reported four cases of gastric ulcer with characteristic pain and in all of them, there was complete achlorhydria. On the other hand, Palmer(1926a) reviewing the literature on peptic ulcer with achlorhydria, concluded that there were no well documented cases on record. He considered that fractional test meals should be done on several occasions before a diagnosis of achlorhydria could be established.

SUMMARY

Three theories of the causation of pain in peptic ulceration have been described. Among my own patients, pain was synchronous with gastric contractions in subjects with duodenal ulcers and was unrelated to contraction in subjects with gastric ulcers. Atropine sulphate gr. 1/50 has been found effective in relieving the pain of peptic ulceration where this has been resistant to dietetic treatment and alkali. The production of free hydrochloric acid after a fractional test meal has been shown to be reduced following a dose of atropine but the emptying time was prolonged. Atropine also diminished the volume of fasting juice. It is probable that these results partly explain the relief of pain produced by this drug in peptic ulceration.

SECTION 9.

THE WATER REVERSAL PHENOMENON.

Welch,(1933) using the condom balloon in the fasting stomach, investigated patients who had clinical evidence of abdominal disturbance. Normal patients showed complete inhibition of hunger contractions when food of almost any kind was introduced into the mouth. In fourteen out of sixteen patients with abdominal disturbance, Welch found, that after the first taste of food, an increase of tone occurred in the stomach with an inhibition of peristalsis. Carlson(1916) showed that cold water, added directly to the stomach by stomach tube, caused an inhibition of hunger contractions for three to five minutes. In the present investigation, it was found that draughts of cold water (four ounces) will cause cessation of the gastric fasting contractions in healthy subjects for at least ten minutes. This experiment was done repeatedly in six patients with normal stomachs, and the time of inhibition of gastric motility varied from ten to thirty-five minutes. The momentary cessation of gastric contractions caused by swallowing a sip of water is shown in Figure 34. The typical result after swallowing four ounces of water is demonstrated in

Method A.

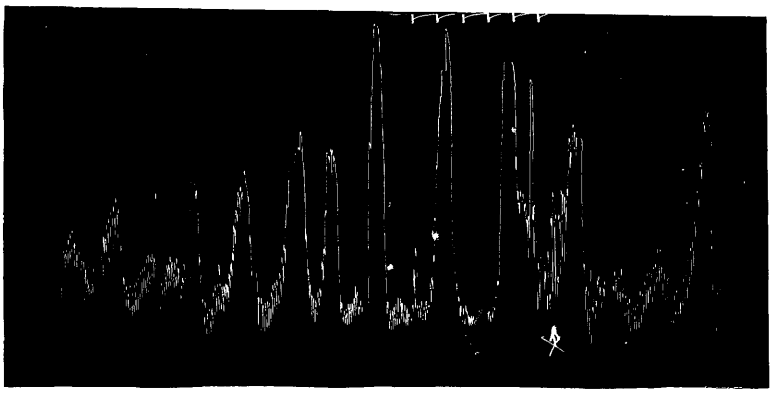


Figure 34.
At x, sip of water given.

Method A.

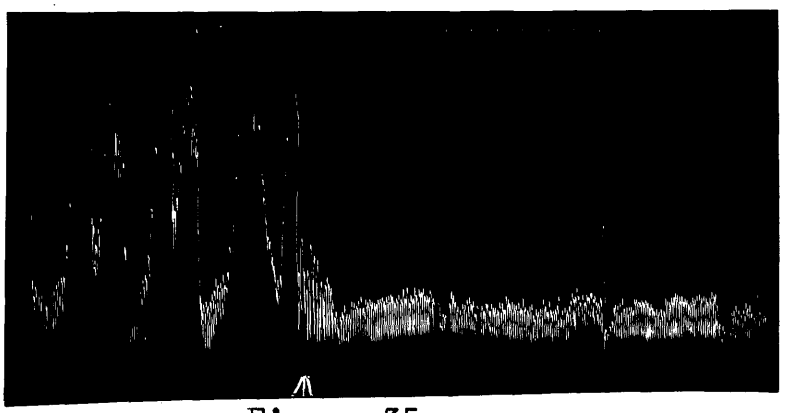


Figure 35.
At arrow, four ounces of water given by mouth.

Method A.

(1)

(2)

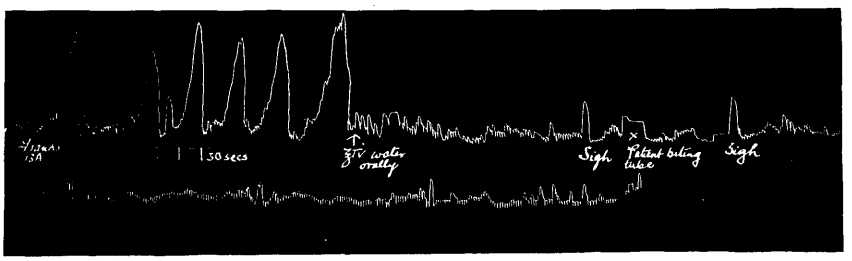


Figure 36.
At arrow, four ounces of water given by mouth in tracing (1).

Figure 35, where there is complete inhibition of contractions for at least ten minutes. The same effect is seen in Figure 36, where powerful contractions in a patient with a normal stomach but hyperchlorhydria, immediately ceased after he had swallowed four ounces of water; in this case the phase of relative quiescence lasted twenty minutes.

In cases of peptic ulceration, a draught of cold water failed to abolish the fasting contractions. Eight cases of peptic ulceration were given four ounces of water and the results are shown in Table I. and in Figures 37, 38, 39 and 40. The case number refers to the brief clinical histories given in Section 7 (b) p.46.

Method A.

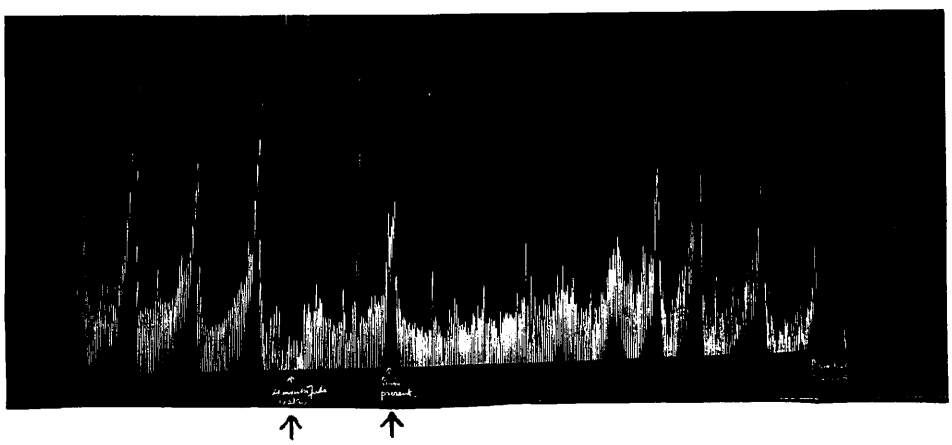


Figure 37.
At first arrow, four ounces of water given.
At second arrow, pain present.

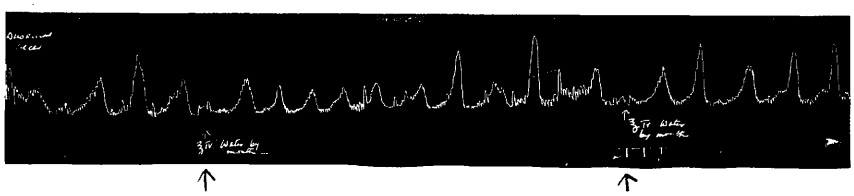
TABLE I.

The Effect on the Gastric Motility of Swallowing a Draught (4 oz.) of Water

Diagnosis		Response
Six normal subjects	-	Immediate inhibition lasting 10-35 minutes.
Acute Duodenal Ulcer (Case I.)	-	Two minutes after water one painful contraction, then three minutes quiescence, followed immediately by powerful gastric contractions (Figure 37).
Acute Duodenal Ulcer (Case II.)	-	No inhibition-immediate onset of tetanic contractions on repeated occasions accompanied by pain (Figure 40). Contractions unaltered by atropine sulphate gr.1/100 subcutaneously given immediately before the water.
Acute Duodenal Ulcers (Cases III. and IV.)	-	No inhibition-contractions continued unaltered. (Figure 38).
Recurrent Duodenal Ulcer (Case VII.)	-	No inhibition-tonus rhythm occurred.
Recurrent Duodenal Ulcer (Case VIII.)	-	No inhibition-contractions continued but of lower amplitude.
Chronic Duodenal Ulcer (Case X.)	-	No inhibition-tonus rhythm for 5 minutes then contractions restarted.
Acute Gastric Ulcer (Case XII.)	-	No inhibition-contractions continued unaltered.

Method B.

I.



Method A.

II.

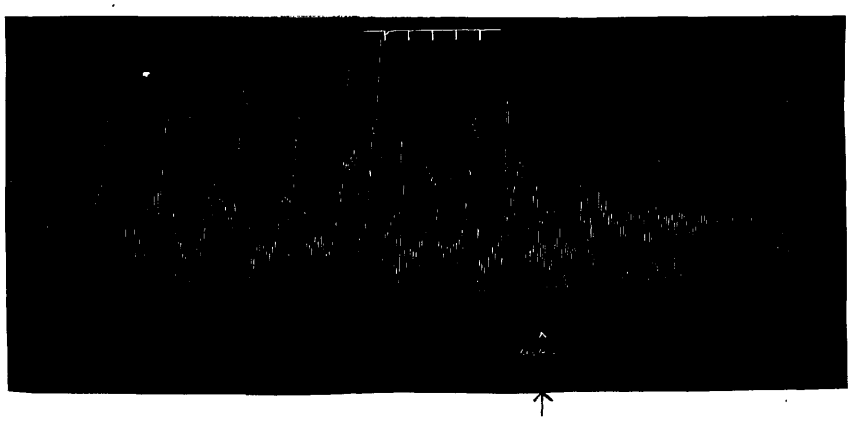


Figure 38.

Tracing I. shows a gastrogram from a patient with an acute duodenal ulcer and on two occasions at the arrows, four ounces of water were given with no effect on the contractions.

Tracing II. shows a normal case with the usual response to four ounces of water given, at the arrow.

Method A.

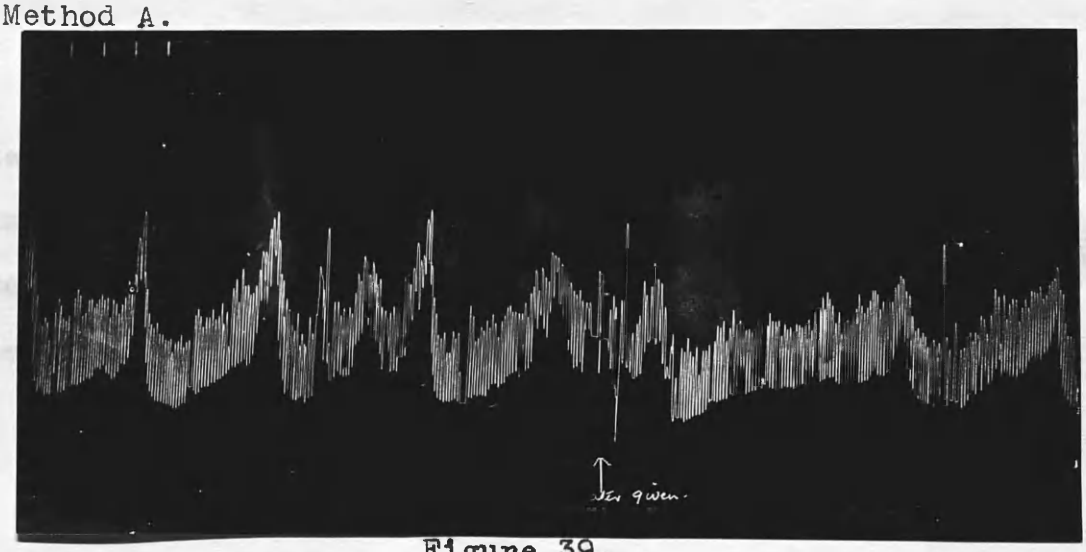


Figure 39.

Acute gastric ulcer - water given at arrow, no cessation of contractions occurred.

Method A.

1.

2.

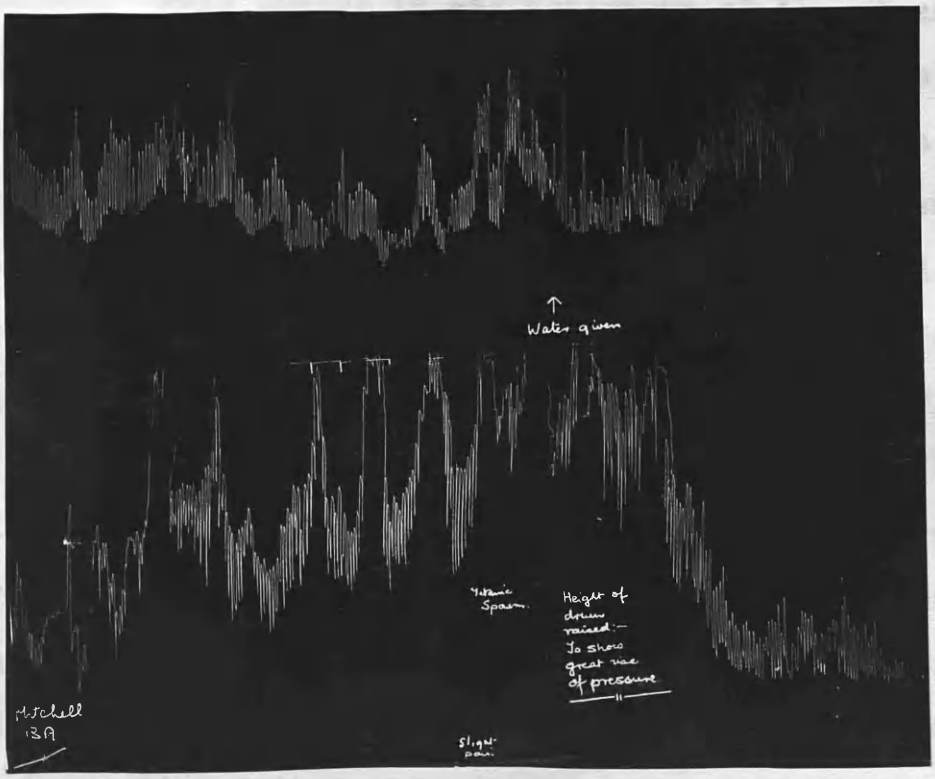


Figure 40.

Acute duodenal ulcer - four ounces of water swallowed at arrow in Tracing 1.
Tracing 2 is a direct continuation of Tracing 1.

It is concluded that the normal inhibition of ten to thirty-five minutes duration, produced by swallowing four ounces of cold water, does not occur in ulcer cases. Instead of this, one of four phenomena may be seen:-

1. Immediately after the patient swallows the water, an intense increase in gastric tone may occur, accompanied by the onset of tetanic contractions.

2. The gastric contractions may continue uninterrupted.

3. The contractions may give place to tonus rhythm.

4. A period of inhibition of very short duration may occur. This happened only once in a series of observations on eight patients.

This change in the behaviour of the stomach, following a draught of water, may be an indication of increased sensitivity of the neuromuscular mechanism to intra-gastric or intra-duodenal stimuli when an ulcer is present. Even gentle stimulation of the ulcerated area is sufficient to cause reflexly either increased contractions of the stomach or the onset of tonus changes instead of the normal period of inhibition. These suggestions have already been made by Carlson,(1917) who postulated an increase sensitivity of the nerve endings in ulcer patients. Hardt(1918) and later Palmer and Heinz(1934) also postulated hyper-irritability of the nerves due to inflammation and considered that this played an essential part in the production of pain in peptic ulceration.

S E C T I O N 1 0

THE RELATION BETWEEN THE SECRETORY ACTIVITY OF THE STOMACH AND THE GASTRIC FASTING CONTRACTIONS

Onodera, et alii, stated that no relationship existed between the degree of gastric acidity and the motor activity of the stomach. Twenty-three cases were investigated in my own series: a fractional test-meal was performed and later the gastric motility was studied by the balloon method.

The degree of acidity was assessed on the basis of the greatest concentration of free hydrochloric acid attained during the fractional test meal and expressed in terms of decinormal acid. The emptying time was judged as the period during which starch remained in the stomach, using the starch-iodide test.

The strength of the contractions, was measured by the amplitude of the wave (mm.) and the breadth of its base (secs.) and the time between individual contractions was noted.

Conclusions (based on results in Table II.): Despite the variation in the acid content of the stomach from marked hyperchlorhydria to complete achlorhydria, the duration of the individual contraction wave is practically

TABLE II.

Case	Amount of free hydrochloric acid expressed in c.cs. of N/10 hydrochloric acid.	Emptying time in hours.	Amplitude of contractions measured in millimetres.	Duration of contractions in seconds.	Interval between individual contractions in seconds.
1.	100	1	40	30	30 - 90
2.	90	2½	24	33	90
3.	85	1½	24	30	30
4.	82	1½	20	33	180
5.	72	2	20	30	30 - 90
6.	70	2½	10	30	120 - 480
7.	70	1½	12	30	30
8.	55	1½	30	35	30 - 90
9.	52	1½	30	35	60
10.	50	2	16	35	90
11.	50	1½	25	40	30
12.	45	1½	30	35	30
13.	45	1½	15	30	45
14.	45	1½	20	30	60 - 90
15.	40	1½	20	30	90 - 270
16.	40	2½	15	30	90
17.	30	1½	15	30	30 - Tetanic stage.
18.	30	1½	16	30	30
19.	30	1½	25	35	45 - 60
20.	30	1	25	30	30 - 45
21.	30	1	15	30	15 - 30
22.	Achlorhydria.	1½	20	30	90
23.	Achlorhydria.	1½	20	30	30

constant - a total variation of 10 seconds being noted in the whole range. No relationship between this figure and the degree of acidity was found. The degree of the gastric acidity and the amplitude of contractions do not appear to be associated.

The marked hyperchlorhydria in Case I. was accompanied by very large contractions (Figure 41), but they were only slightly bigger than those in Case 9, with approximately half the degree of acidity.

Method B.

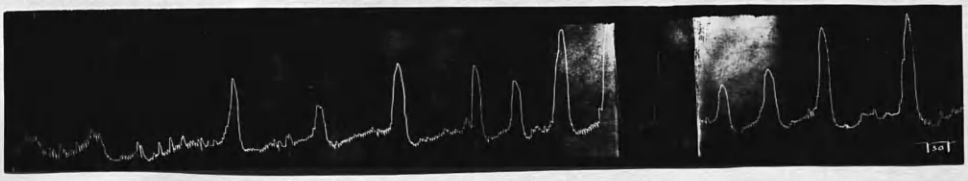


Figure 41.

Method B.

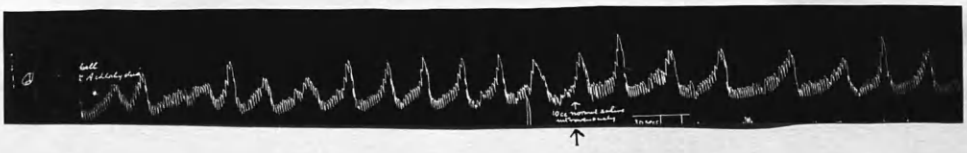


Figure 42.
At arrow 10c.cs. normal saline given intravenously.

Figure 42 shows that even with achlorhydria (Case 23) well-marked gastric contractions were found.

The interval between individual contractions varies from the tetanic state (where no true pause can be said to exist) to a maximum rest period of about eight minutes. This interval is not related to the degree of acidity but varies from one person to another.

The emptying time of the stomach, the amplitude and duration of contractions, and the interval between contractions appear to be unrelated to one another.

PART 2.

SECTION 1.

THE ACTION OF DRUGS ON THE MOTILITY OF THE FASTING STOMACH.

The Method of Assessing Drug Action:

Certain factors must be kept in mind during any investigation on the action of drugs on the contractions of the empty stomach. Sachs,(1936) in experiments with drugs acting on the vegetative nervous system, stated - "the concentration, dose and mode of application of the drug, the tonus and excitability of the innervated organs and the state of the whole autonomic system, central and peripheral, must be taken into consideration".

In the following experiments, the drugs were given either by subcutaneous, intramuscular or intravenous injection. The action of the drug was studied on different phases of gastric activity. The patient, who had been previously trained to swallow the balloon, was in a state of contentment. If any difficulty was encountered in passing the balloon, the experiment was abandoned.

Drugs may have varying effects on gastric motility according to conditions existing at the time of

administration. If the stomach is showing active hunger contractions (Phase I.), the action of a drug may be:- (a) to stop them, or (b) to increase their frequency or amplitude, or (c) to leave them unaltered. The result of a single experiment would be worthless, as these periods of contractions are self-limiting and while normally lasting a half to one hour, the contraction phase might be ending spontaneously at the time of administration of the drug.

The following general rules have been adopted to assist in drawing conclusions from the results of the various investigations. If a drug given early in Phase I. (hunger contraction phase) coincides on every occasion with a cessation of contraction, it seems fair to conclude that the drug has a sedative action on gastric motility. It has been found that in the middle of a phase of hunger contractions, the interval between the contractions is of the same duration. The tetanic phase (Phase IV.) is very rarely seen, so that if a drug which is given early in Phase I. constantly produces an increase in the frequency and amplitude of contractions, it is concluded that the drug has a stimulating action on gastric motility. The period of tonus change (Phase II.), while frequently the precursor to true gastric contractions, may pass into

relative quiescence (Phase III.) without the occurrence of gastric contractions. If a drug given in a period of tonus change repeatedly causes this to pass into Phase I. (hunger contractions) then this drug is assumed to have an excitatory action. No conclusion, however, can be drawn if the tonus changes disappear. Any drug given in Phase III. (relative quiescence), which in repeated experiments is followed by the onset of gastric contractions, is assumed to have a stimulating action.

A distinction must be made between drugs powerful enough to cause new gastric contractions during a phase of relative quiescence and those merely augmenting or increasing the frequency of hunger contractions already established. There are thus several degrees of excitatory action.

The actual effect of the injection appears to be of no significance. Control injections of normal saline (10 c.c.) intravenously did not affect gastric motility. (Figure 42).

In many of the figures shown in this portion of the thesis, two or more tracings are seen in the same photograph. These are marked Tracing 1. and Tracing 2., and in every case the second tracing is a direct continuation of the first.

S E C T I O N 2.

The Action of Atropine:

It is generally accepted that atropine paralyses the post-ganglionic fibres of the parasympathetic system, or, as Fraser(1938) explains, prevents the effect of the liberated acetylcholine. Among many other results, this action should produce (a) a quickening of the heart-rate, and (b) a reduction of gastric motility, as both these effects are due to paralysis of the nerve endings of the vagus.

In the isolated stomach of a dog, Zunz and Tysebaert(1926) found only weak contractions after 1 mg. of atropine per kilo. Bastedo(1932) quotes Ginsburgh and Tumpowsky, who found that 0.8 - 1.5 mg. (1/80 - 1/40 gr.) inhibited the hunger contractions of dogs; and noting the same effect when the splanchnic nerves to the stomach were cut, they concluded that the action was purely peripheral. In man, Lasch(1922) stated that increased peristalsis was in most cases inhibited by atropine but no cessation of normal movements was found. This experiment was performed by means of x-ray apparatus and repeated barium meals. Tetelbaum,(1926) using the balloon method with fasting patients, found that 0.3 - 0.5 mg. of atropine stopped contractions of the pyloric part, although sometimes a

larger dose was necessary. He stated that 0.3 - 0.5 mg. had no effect on the peristalsis produced by food; 1 mg. of atropine was necessary for this.

Rall,(1926) by the same method, noted that twenty drops of 1/1000 solution of atropine sulphate (1.2 mg.) orally, caused a diminution in gastric motility and prevented backflow of bile into the stomach. The normal spasm of the pylorus was not inhibited and subcutaneous administration was found more effective than the oral route.

Neidhart(1933) in his first series of experiments, stated that 0.5 mg. of atropine sulphate subcutaneously had no constant effect. In a second series (1935) he found that 0.3 mg. intravenously reduced gastric contractions; 0.5 mg. intravenously produced a short period of paralysis and 0.7 mg. more prolonged paralysis.

Danielopolu,(1930) using the intravenous route, described experiments in which 0.05 mg. caused increased tone and amplitude of gastric contractions; 0.25 mg., if given when the contractions were maximal, lowered tonus and stopped movement. The hypermotility with very small doses was accompanied by a slowing of the heart-beat.

In the present investigation, the range of dosage was 0.05 mg. to 2 mg. of atropine sulphate. Both subcutaneous and intravenous routes of administration were

used, and the action was studied in healthy subjects and in patients with gastric disease. The first range of dosage employed was 0.05 - 0.3 mg. (gr.1/1200 - gr.1/200), by intravenous injection. Then the effect of 0.4 - 1 mg. (1/150 - 1/60 grain) by intravenous injection was studied. Thirdly, 0.6 - 2 mg. (1/100 - 1/33 grain) was given by subcutaneous injection, and lastly, the effect of atropine on the pulse-rate was noted.

(a) The Effect of Small Doses of Atropine:

The effect of small doses of atropine - 0.05 mg. to 0.3 mg. intravenously was tried in eight subjects. These patients had no complaint referable to the gastro-intestinal tract and on x-ray examination showed no abnormality of the stomach. The effects on the gastric contractions and on the pulse-rate are shown in Table III., and a typical result is shown in Figure 43.

Method A.

Figure 43.
At arrow, Atropine Sulphate 1/20 mg. given intravenously.

TABLE III.

Action of Atropine Sulphate 0.05 to 0.3 mg. Intravenously.

Case	Dose	Action on Pulse-rate	Effect on Gastric Motility
1.	.05 mg.	Slowed in 10 mins. by 7 beats/min.	Given during hunger contractions - immediate increase and augmentation of contractions.
2.	.1 mg.	Slowed in 5 mins. by 8 beats/min.	Given during tonus changes - in 4 mins. increased to gastric hunger contractions.
3.	.1 mg.	Slowed in 5 mins. by 10 beats/min.	Given during hunger contractions - immediate increase in frequency and amplitude.
4.	.1 mg.	Slowed in 5 mins. by 7 beats/min.	Given during hunger contractions - slight immediate increase in frequency.
5.	.1 mg.	Not taken.	Given during tonus change - in 7 mins. onset of typical hunger contractions.
6.	.1 mg.	Slowed in 5 mins. by 10 beats/min.	Given during relative quiescence - no contractions produced.
7.	.2 mg.	Slowed in 5 mins. by 3 beats/min.	Given during hunger contractions, continued unaltered for 10 mins. then slight increase in amplitude and frequency of contraction.
8.	.3 mg.	Not taken.	Given during weak contractions in 10 mins. contractions which had continued became much stronger.

It is clear that atropine by the intravenous route in doses of from 0.05 to 0.3 mg. produces - (a) a slowing of the heart-rate, and (b) a stimulating action on gastric motility. If hunger contractions are present these are augmented and increased in frequency. If the stomach is undergoing tonus change, this is converted into more active gastric contractions. In one case, however, during a period of quiescence no contraction was produced.

(b) The Effect of Atropine in Dosage of 0.4 mg. to 1 mg. by Intravenous Injection:

The next investigation consisted of the administration of atropine 0.4 mg. intravenously to three normal subjects. (Table IV.)

T A B L E IV.

Action of Atropine Sulphate 0.4 mg. Intravenously.

Case	Action on Pulse-rate	Action on Motility
1.	Quickened by 20 beats/min. in 5 mins. after injection.	Given during hunger contractions - immediate cessation.
2.	Quickened by 24 beats/min. in 5 mins.	Given during hunger contractions - immediate cessation.
3.	Quickened by 18 beats/min. in 5 mins.	Given during hunger contractions - immediate cessation.

Atropine 0.4 mg. intravenously appears to have a sedative action on gastric motility accompanied by a quickening of the pulse.

T A B L E V.

Action of Atropine 0.6 mg. Intravenously.

Case	Action on Pulse-rate	Action on Motility
1.	Quickened by 8 beats/min. in 5 mins.	Given during hunger contractions - immediate cessation.
2.	Quickened by 19 beats/min. in 5 mins.	Given during hunger contractions - immediate cessation.
3.	No quickening - slight slowing 4 beats/min. 5 mins. after injection. Normal in 30 mins.	Given during hunger contractions - immediate cessation of stomach movements lasting 30 mins.

It is seen in Table V. that 0.6 mg. of atropine sulphate given intravenously to three normal patients appears to have an inconstant action on the heart but a constant sedative effect on the gastric motility. Quickening of the pulse seems to be the most usual action, but it is interesting to note that in Case 3, slowing of the pulse was associated with an immediate cessation of hunger contractions. (Figure 44).

Method B.

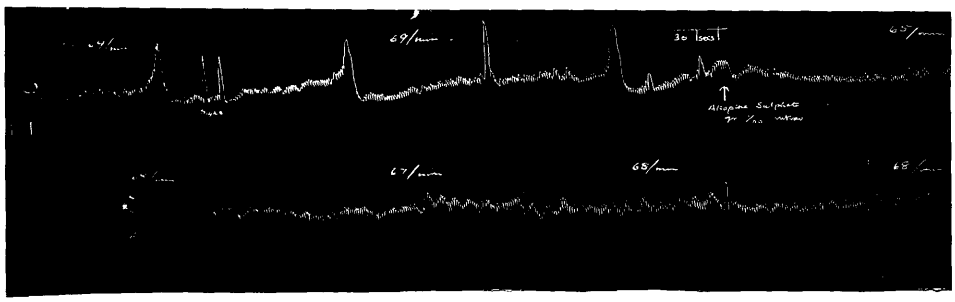


Figure 44.
Atropine gr.1/100 given intravenously at arrow.

Finally, atropine sulphate 1 mg. was given intravenously to one normal subject. There was immediate and complete cessation of gastric motility. The pulse-rate immediately increased by 27 beats/per minute in five minutes, thereafter gradually falling to the pre-injection level. These are the effects with which the clinician is familiar when he gives atropine sulphate in its maximum official dose.

It can be seen at this stage that there are two widely differing actions of atropine: - (i) with very small doses, a stimulant effect on gastric motility and a slowing on the heart-rate and (ii) with larger doses,

a sedative action on gastric motility with a quickening effect on the pulse-rate.

(c) The Action of Atropine in Dosage of 0.6 to 2 mg. by Subcutaneous Injection:

The action of atropine in doses of 0.6 to 2 mg. (1/100 - 1/33 grain) by subcutaneous injection was next investigated because the drug is commonly used therapeutically in these doses to relieve spasm. Normal subjects and patients with peptic ulcer were investigated. The data in Table VI. show the action of atropine sulphate 0.6 mg. by subcutaneous injection, on the pulse-rate and gastric motility.

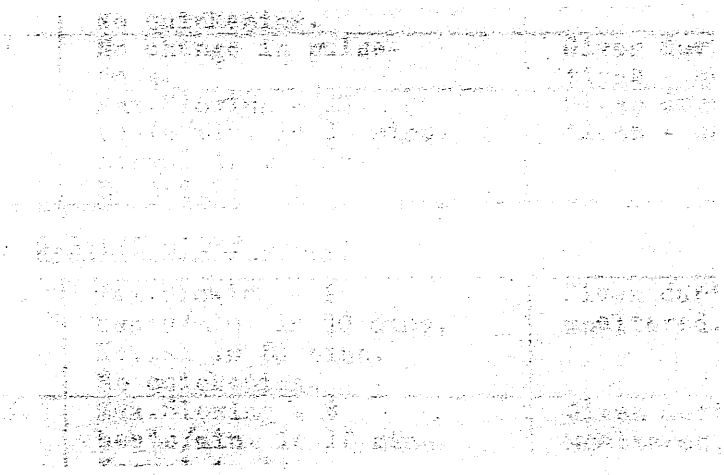


TABLE VI.

Action of Atropine Sulphate 0.6 mg. (1/100 gr.) Subcutaneously on the Pulse-rate and Gastric Motility.

A. NORMAL CASES:

	Action on Pulse-Rate	Effect on Gastric Motility
1.	Max.Slowing - 10 beats/min. in 15 mins. Normal in 45 mins. No quickening.	Given during relative quiescence - in 10 mins. onset of active gastric contractions.
2.	Max.Slowing - 7 beats/min. in 10 mins. Max.Quickening + 5 beats/min. in 30 mins. Normal in 1 hr. 10 mins.	Given during hunger contractions - slight increase in frequency and strength.
3.	Max.Slowing - 8 beats/min. in 10 mins. Normal in 40 mins. No quickening.	Given during hunger contractions - these continued for 3 mins. then 20 mins. quiescence, then increased contractions.

B. DUODENAL ULCER CASES:

1.	Max.Slowing - 10 beats/min. in 15 mins. Normal in 40 mins. No quickening.	Given during relative quiescence - 15 mins. later active hunger contractions after preliminary tonus change.
2.	No change in pulse-rate.	Given during tonus change - 5 mins. later active hunger contractions.
3.	Not taken.	Given during weak contractions in 6 mins. became very powerful and continued for 35 mins.
4.	Max.Slowing - 4 beats/min. in 15 mins. Normal in 40 mins. No quickening.	Given during hunger contractions - no change produced.
5.	No change in pulse-rate.	Given during hunger contractions - no change produced.
6.	Max.Slowing - 10 beats/min. in 15 mins. Normal in 50 mins. No quickening.	Given during hunger contractions - cessation in 4 mins.

C. GASTRIC ULCER CASES:

1.	Max.Slowing - 6 beats/min. in 10 mins. Normal in 50 mins. No quickening.	Given during tonus change - unaltered.
2.	Max.Slowing - 8 beats/min. in 15 mins. Normal in 50 mins. No quickening.	Given during tonus change - unaltered, slight pain present not relieved by atropine.

Method A. Gastric Ulcer.

1.

2.

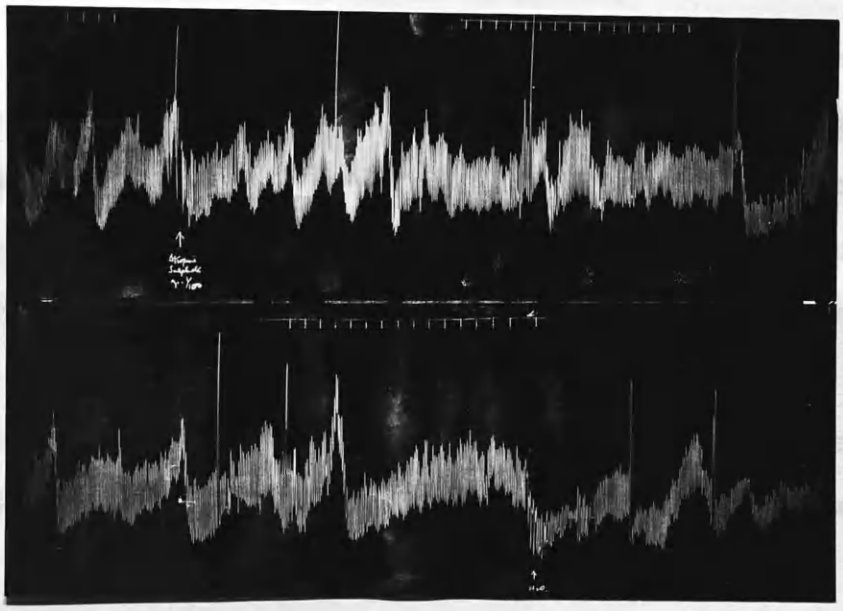


Figure 45.

At arrow, Atropine Sulphate gr.1/100 given subcutaneously in Tracing 1.

Method A. Duodenal Ulcer.

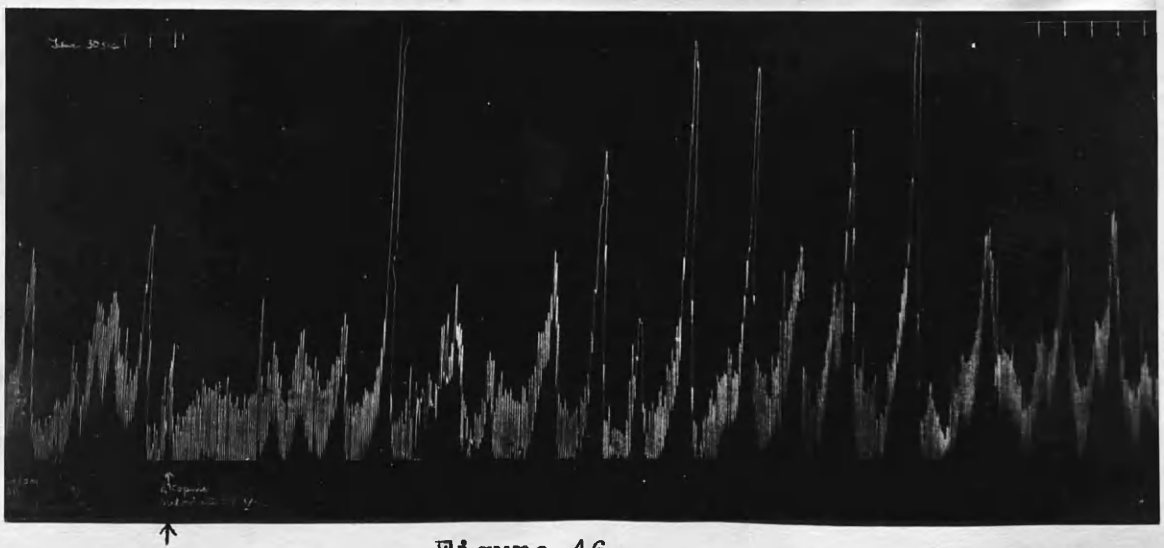


Figure 46.

At arrow, Atropine Sulphate gr.1/100 given subcutaneously.

Typical tracings (Figures 45, 46) are shown illustrating the results set out in Table VI. page 96. In two normal subjects atropine apparently produced hunger contractions but in one experiment there was cessation of gastric motility. In patients with duodenal ulcer, the results were similar to those obtained in normal subjects; but here again the effect was inconstant. The action was usually excitatory, occasionally there was no change and once the action was sedative.

In the gastric ulcer cases, there was no change in motility produced by the injection of atropine sulphate gr. 1/100. In one case, pain present was not relieved.

In this small series, the action of 0.6 mg. (gr.1/100) of the drug subcutaneously on the pulse-rate was to cause slowing within 15 minutes of 5-10 beats per minute; this rate usually returned to its previous level in 40 to 70 minutes. Rarely, this dose of atropine was without effect, and on one occasion it produced slight quickening after a preliminary period of slowing.

A subcutaneous injection of 1 mg. was given to one normal person with no effect on the pulse-rate. It was administered during a period of hunger contractions and these continued; they appeared to be slightly stronger

after the injection. (Figure 47).

Method A.

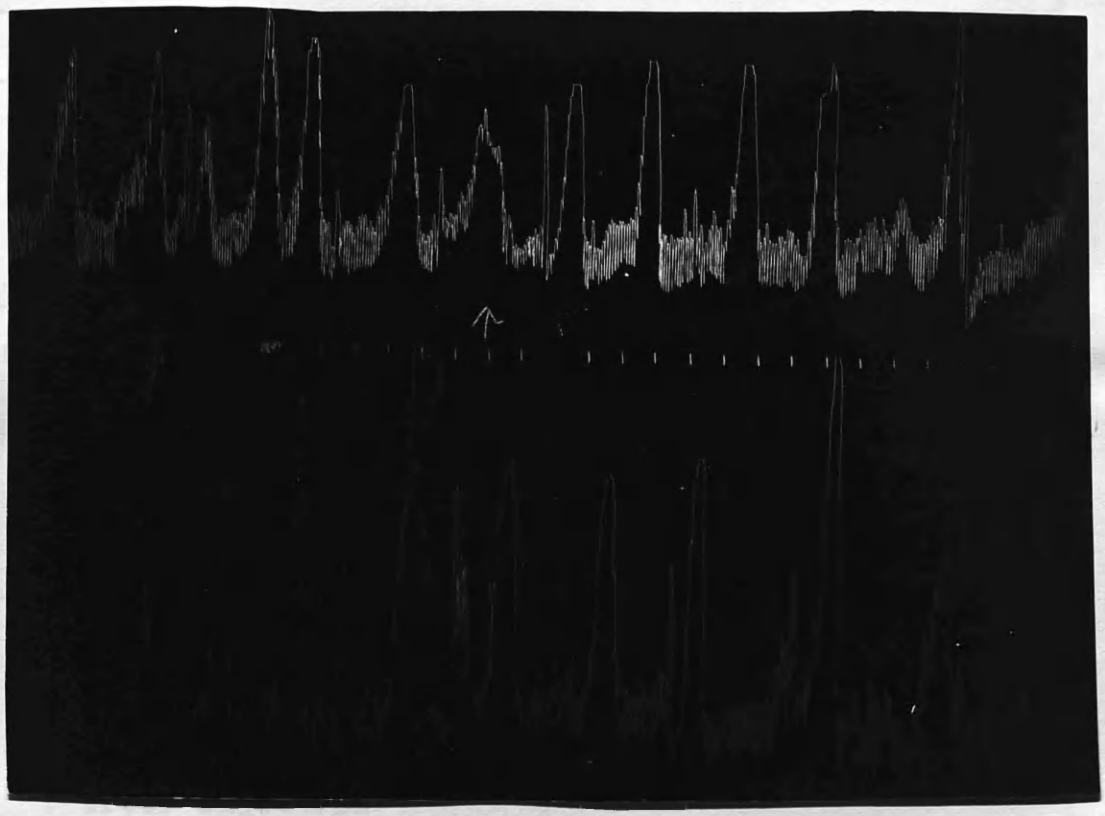


Figure 47.

Atropine Sulphate gr. 1/60 subcutaneously given at arrow in Tracing 1.

In the next series, atropine was given in dosage of 1.2 mg. (1/50 grain) subcutaneously to five normal subjects. The results are tabulated in the following page. (Table VII.)

TABLE VII.

Action of Atropine Sulphate 1.2 mg. Subcutaneously on the Pulse-Rate and Gastric Motility.

NORMAL CASES		
	Action on Pulse	Action on Gastric Motility
1.	Preliminary slowing, 10 mins. after injection of 2 beats/min. Then quickening, max. 40 mins. after injection + 13 beats/min.	Given during hunger contraction - stopped 16 mins. after injection.
2.	Preliminary slowing, 10 mins. after injection of 2 beats/min. Then quickening, max. + 24 beats/min. 45 mins. after injection. Pulse-rate not normal in 1½ hours.	Given during hunger contraction - stopped 5 mins. after injection for at least 1½ hours.
3.	Preliminary slowing 5 mins. after injection of 2 beats/min. Then quickening, max. + 22 beats/min. 35 mins. after injection. Pulse-rate not normal 1½ hrs. after injection.	Given at onset of a period of hunger contraction - stopped in 12 mins. for at least 1½ hours after injection.
4.	Preliminary slowing 10 mins. after injection of 4 beats/min. Then quickening, max. + 32 beats/min., 40 mins. after injection.	Given at onset of a period of hunger contractions - cessation 20 mins. after injection.
5.	No slowing. Max. quickening + 28 beats/min. 30 mins. after injection. Pulse-rate not normal 2 hrs. 5 mins. after injection.	Given during hunger contraction - stopped 2 mins. after injection for 2 hrs. 15 mins. at least.

The action of atropine 1.2 mg. (grain 1/50) on the pulse-rate and gastric motility may be summarised thus: After a period of preliminary slowing of the pulse-rate of 2-4 beats per minute within ten minutes of injection, quickening of the pulse occurred ranging from 13-32 beats per minute in from thirty to forty-five minutes after the injection. In all cases a cessation of gastric contractions occurred, but the time of disappearance varied from two to twenty minutes after the injection. (Figure 48).

Method A.

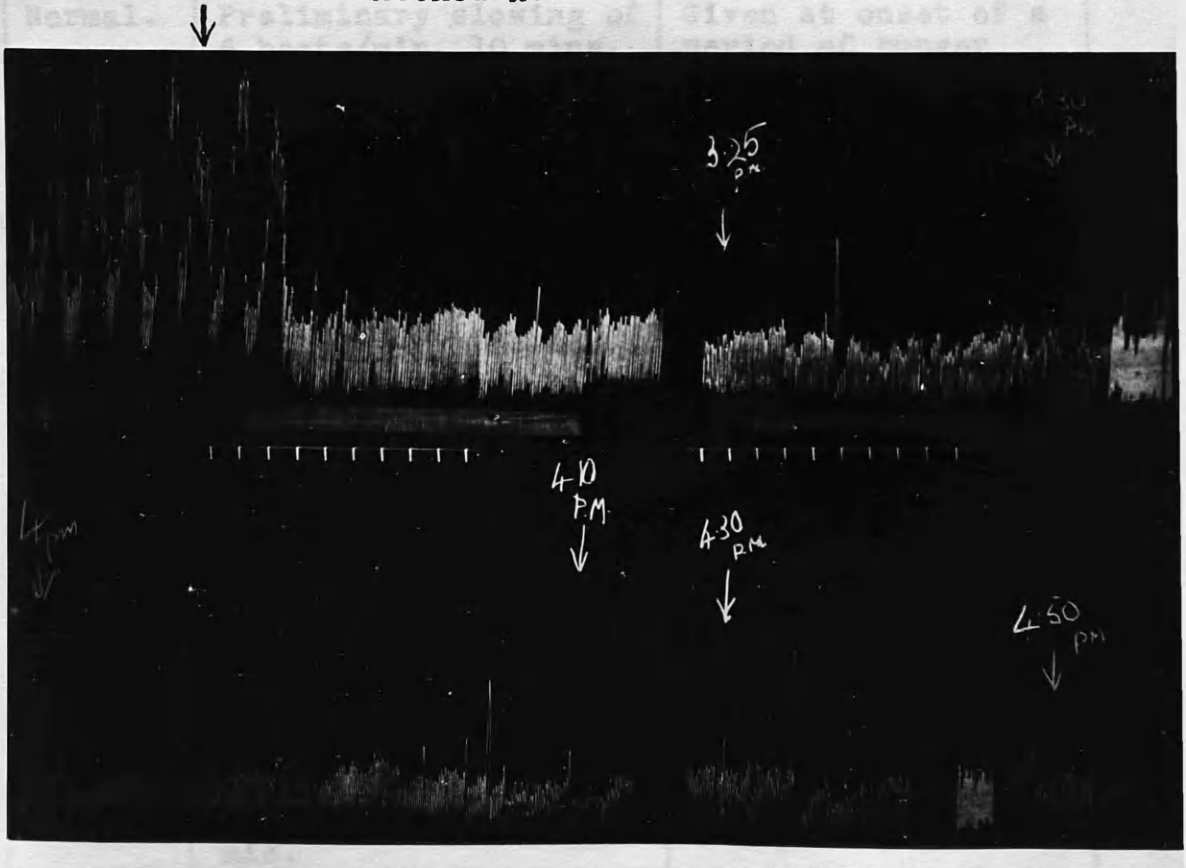


Figure 48.
At the arrow in Tracing 1, Atropine Sulphate gr. 1/50 given subcutaneously.

The action of atropine 2 mg. given by subcutaneous injection was next studied in a patient with a normal stomach and in patients with a gastric and a duodenal ulcer. The results obtained are shown in Table VIII.

T A B L E VIII.

The Action of Atropine 2 mg. on the Pulse-Rate and Gastric Motility given by Subcutaneous Injection.

Case	Action on Pulse-Rate	Action on Gastric Motility
Normal.	Preliminary slowing of 6 beats/min. 10 mins. after injection. Then quickening, max. + 38 beats/min. 45 mins. after injection.	Given at onset of a period of hunger contractions - cessation in 13 minutes.
*Duodenal Ulcer.	Preliminary slowing of 8 beats/min. 10 mins. after injection. Then quickening, most marked 40 mins. after injection + 24 beats/min.	Given at start of period of hunger contractions - within 10 mins. complete cessation of contractions lasting at least 45 mins.
*It should be noted that this case of duodenal ulceration was one in which atropine gr. 1/100 appeared to produce active hunger contractions.		
Gastric Ulcer.	Preliminary slowing of 8 beats/min. 5 mins. after injection. Then quickening most marked 45 mins. after injection of + 13 beats/min.	Given during hunger contractions - complete cessation after 4 mins. lasting 1 hour at least.

It was found that the action of atropine on the normal and on the ulcer cases was identical (Figures 49, 50, 51). In all cases a preliminary slowing of the pulse-rate amounting to 6-8 beats per minute occurred within ten minutes of atropine administration, and forty to forty-five minutes after the injection a quickening of the pulse-rate of 13-38 beats per minute was noted. The effect of this dose of atropine on gastric motility was complete cessation of contractions four to thirteen minutes after the injection, lasting as long as the experiments were continued.

Method A. Normal Case.

1.

2.

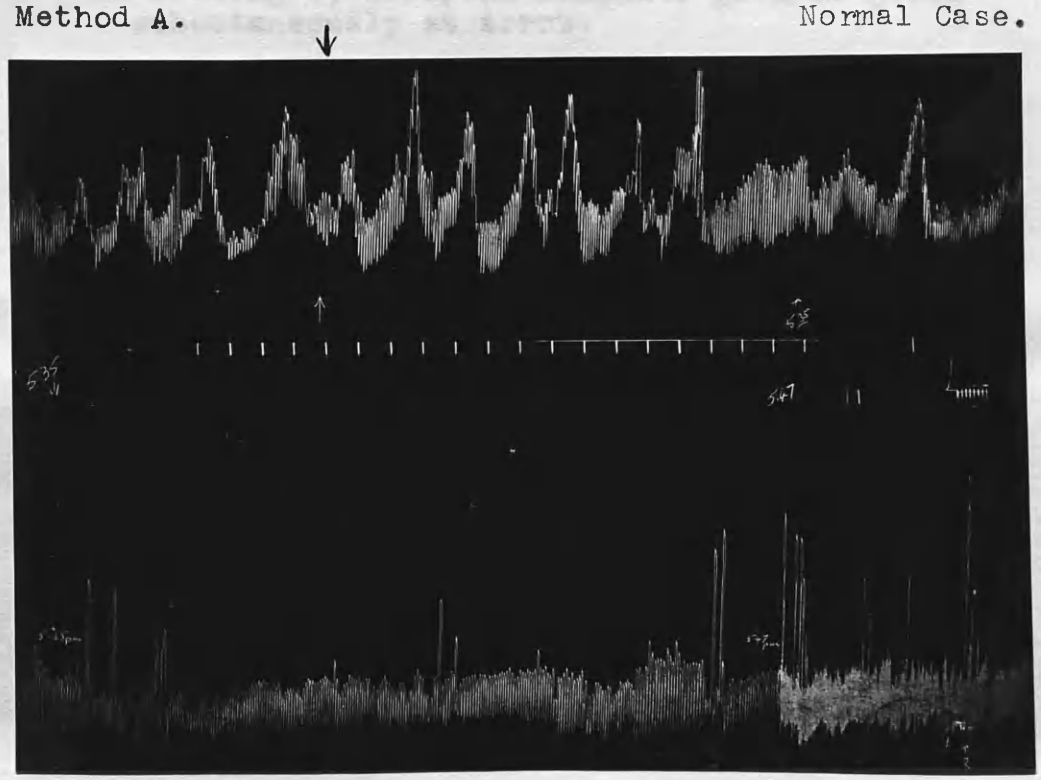


Figure 49
At arrow in Tracing 1, Atropine Sulphate gr.1/33 given subcutaneously.

Method B. Duodenal Ulcer.

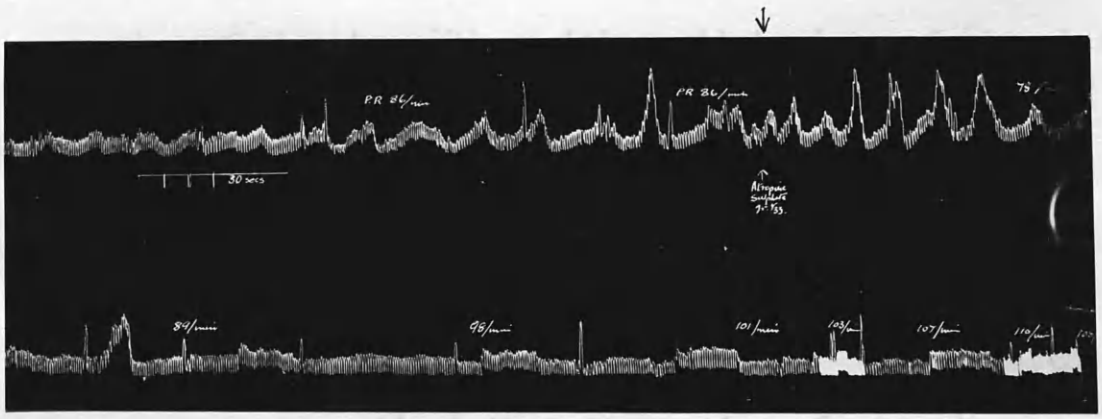


Figure 50.

In Tracing 1, Atropine Sulphate gr.1/33 given subcutaneously at arrow.

Method B. Gastric Ulcer.

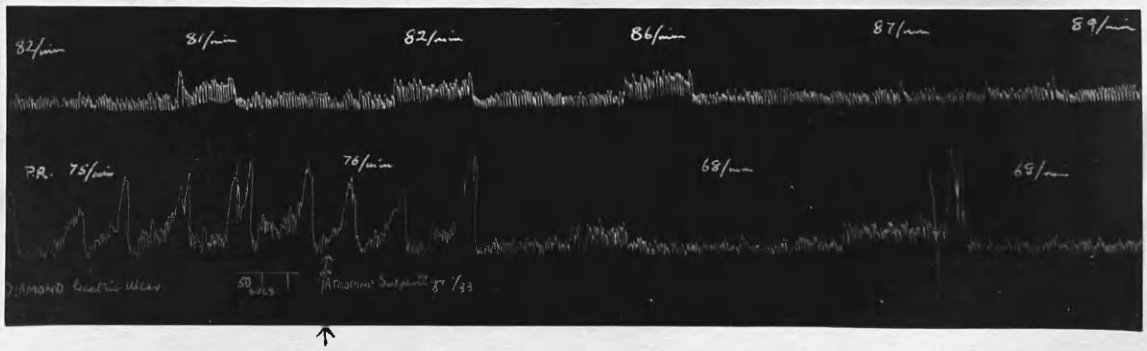


Figure 51.

At arrow in Tracing 1, Atropine Sulphate gr.1/33 given subcutaneously.

Summarising the findings at this stage, it is seen that (1) small doses at atropine (0.05 - 0.3 mg.) intravenously stimulate the movements of the stomach and slow the pulse-rate, (2) an intermediate dose of atropine (0.6 mg.) subcutaneously has an inconstant effect, more usually excitatory, on the gastric contractions and in most cases slow the pulse, (3) large doses of atropine (1.2 - 2 mg.) by hypodermic injection cause complete cessation of the stomach movements and quicken the pulse.

It is evident that the action of atropine on the pulse-rate runs parallel with the effect on the gastric motility.

(d) The Effect of Atropine on the Pulse-Rate:

The action of atropine on the pulse-rate was investigated thus: (a) 0.05 to 0.1 mg. intravenously, (b) 0.6 mg. subcutaneously, and (c) 1-2 mg. subcutaneously.

(a) The action of small doses of atropine, 0.05 to 0.1 mg., on the pulse-rate is shown in Table IX. Three subjects were given 0.05 mg. intravenously and in all of them slowing of pulse-rate amounting to 3-9 beats per minute occurred. The pulse-rate had almost returned to normal in thirty minutes. With 0.1 mg. by intravenous dosage, four subjects all showed a fall in pulse-rate of 7-12 beats per minute. 1 c.c. of saline was given

intravenously as a control, the pulse-rate being taken as with the atropine. The graphs (Figure 52) show the average results with 0.05 and 0.1 mg. respectively. It is seen that small doses of atropine produce slowing of the pulse-rate.

T A B L E IX.

Minutes	Pulse-rate 1 2 3	Pulse-rate 1 2 3	Control	Average Readings	
10	73 70 66	83 63 66	74	69	70
5	73 70 66	83 63 66	71	69	70
0	Atropine mg.1/20	Atropine mg.1/10	Saline 1 c.c.	Atropine mg.1/20	Atropine mg.1/10
5	70 68 61	73 56 62	72	66	63
10	69 67 59	73 56 62	71	65	64
15		71 59 61	71		68
20	64 67 60	71 59 62	73	63	68
25			72		
30	73 68 60		73	67	

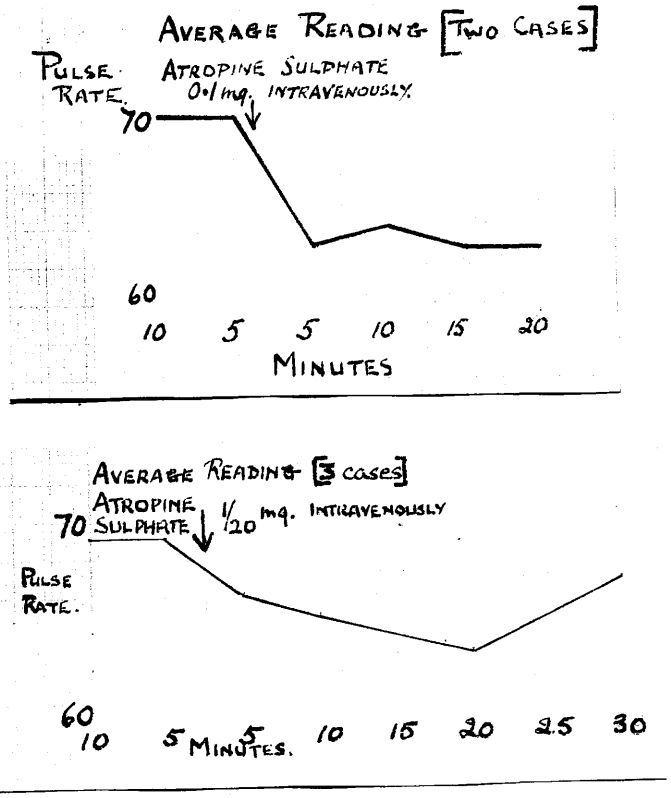


Figure 52.

(b) Table X. shows the results obtained from the action of atropine sulphate 0.6 mg. by subcutaneous injection. In four subjects, instead of the atropine, saline 1 c.c. by subcutaneous injection was used as a control. In each case, two pulse-rate readings were taken at an interval of five-minutes before the atropine or the water was given. In twenty-three cases, the pulse-rate was taken at intervals of fifteen minutes for periods of thirty to ninety minutes. In another group (fourteen cases,) the pulse-rate was observed at five-minute intervals for thirty to sixty minutes. The

results are seen in Figures 53 and 54.

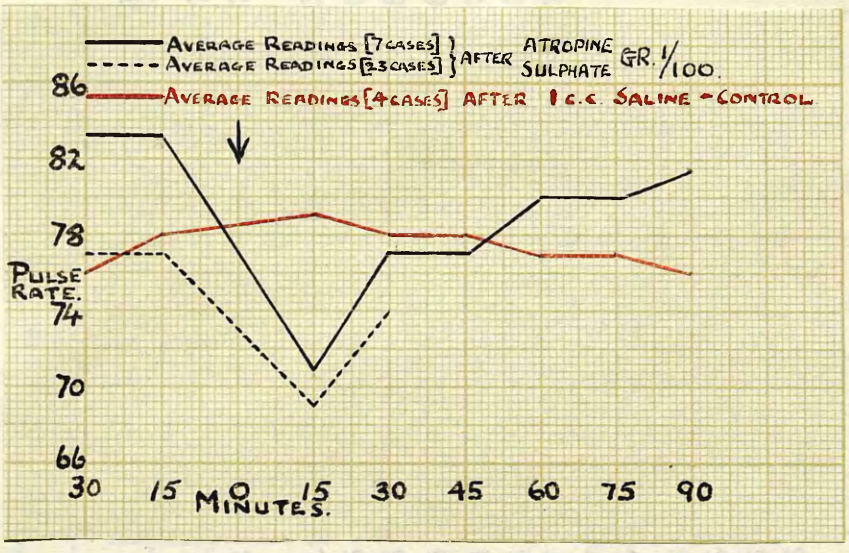


Figure 53.

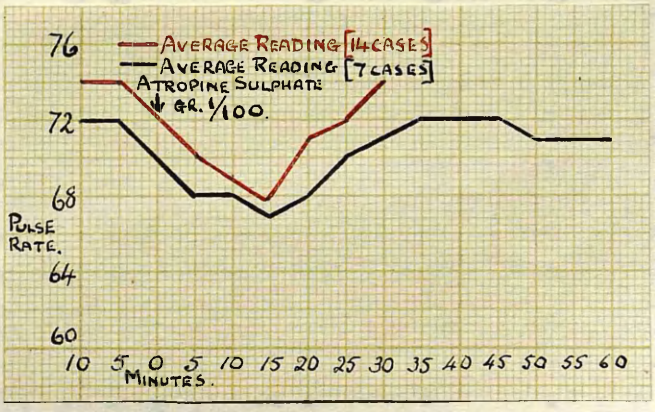


Figure 54.

TABLE X.

Minutes	PULSE - RATES																							
	1	2	3	4	1	2	3	4	5	CASE 6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
10	77	70	74	90	72	104	84	80	80	78	84	60	71	68	69	84	80	72	65	90	70	76	75	73	69	66	82
5	77	74	71	92	72	100	84	80	81	79	86	61	72	68	69	84	80	73	64	91	70	77	75	72	69	66	82
0		Saline 1 c.c.																									
												Atropine sulphate gr. 1/100 subcutaneously															
5												55	65	60	65	84	79	73		90	67	70	68		65	64	82
10												53	65	60	68	80	78	71		90	62	68	67		68	62	76
15	79	76	71	92	66	82	70	68	70	66	76	53	65	60	68	76	78	71	61	90	62	66	66	69	68	62	76
20												58	74	62	67	77	70	70		86	76	66	71		68	70	82
25												59	75	63	67	79	76	71		82	80	68	74		68	70	84
30	80	70	73	92	76	90	80	68	78	70	80	60	77	64	68	79	78	72	60	90	90	70	74	73	68	70	90
35												61	77	64	68	80	80	74									
40												61	77	64	68	80	80	77									
45	79	70	70	94	74	90	82	67	78	74	80	61	76	64	67	80	80	76									
50												61	75	64	67	81	80	75									
55												61	75	64	68	80	80	74									
60	77	69	69	94	80	90	82	68	90	76	80	61	75	64	68	80	80	74									
65																											
70																											
75	79	70	69	92	80	90	83	70	86	78	78																
80																											
90	77	70	68	92	80	86	84	74	84	79	80																

From the table and graphs it will be seen that twenty-two of the twenty-three patients showed a fall in pulse-rate fifteen minutes after atropine administration. In one case no change occurred. This slowing exceeded five beats per minute in fifteen of the subjects. It is noteworthy that the reduction of the pulse-rate appeared within the first fifteen minutes of the injection.

After one hour, eight out of fourteen patients showed a pulse-rate less than that which preceded the administration of atropine; in four of the subjects the pulse-rate had increased, and in two, it had reached its initial value. Seven patients were observed for ninety minutes, and at that time three still showed a reduction of 4-14 beats per minute; in two, an increase of 3 and 8 beats per minute was noted, and in the last two, the initial rate was recorded.

It is concluded that 0.6 mg. (1/100 gr.) of atropine sulphate usually produces slowing of the pulse-rate which seldom lasts less than ninety minutes.

(c) The effect of administration of one milligram (1/60 gr.) of atropine on the pulse-rate was next observed on five subjects. Readings were taken at fifteen minute intervals for ninety minutes (Table XI.), and the average

curve was obtained. (Figure 55)

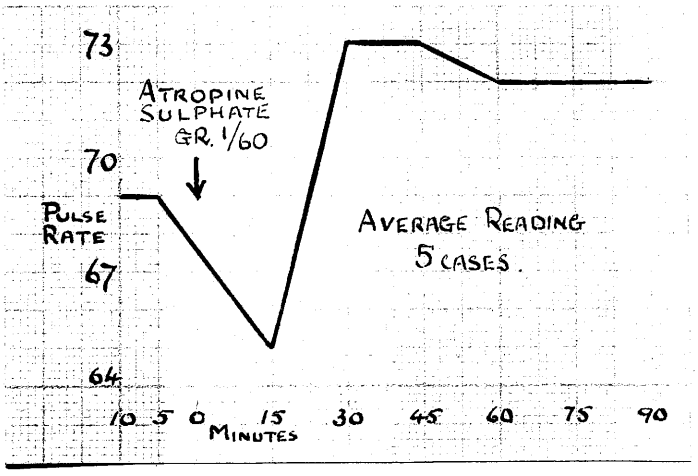


Figure 55.

T A B L E XI.

Minutes	Pulse-rates				
10	70	78	69	60	72
5	70	78	68	60	72
0	Atropine gr. 1/60 sub-cutaneously				
15	74	60	64	60	70
30	78	76	84	60	68
45	78	78	84	62	66
60	78	78	78	59	68
75	78	78	78	60	70
90	78	80	78	60	68

After fifteen minutes, three of the five patients showed a fall in pulse-rate of two to eighteen beats per minute; in one an increase occurred and in the last there was no change.

In two cases the reading after one hour showed a rise of 8 and 10 beats per minute respectively; in two other cases a fall of 1 and 4 beats per minute respectively, and in the remaining one, there was no alteration.

At ninety minutes, a quickening of 2 to 10 beats per minute was noted in three cases, in one no change occurred, and in the last a slowing of 4 beats per minute persisted.

In this dosage, atropine has usually the effect of producing an initial slowing followed by a slight increase in the pulse-rate.

With 1.3 milligrams (1/50 grain) of atropine, while slight preliminary slowing is present in two out of four cases, as shown in Table XII., the usual and important feature is a marked increase in the pulse-rate. (Figure 56).

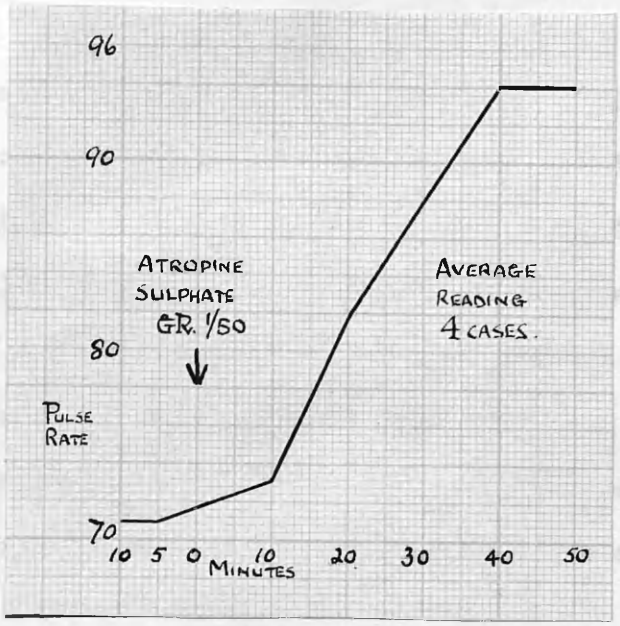


Figure 56.

TABLE XII.

Minutes	Pulse-Rate						
10	60	63	90	72	94	75	86
5	60	63	90	72	94	76	86
0	Atropine gr.1/50 subcutaneously				Atropine gr. 1/33 subcutaneously		
5	60					68	78
10	72	62	86	72		68	80
15					88	79	89
20	88	74	96	70		82	98
25						82	98
30	87	82	110	74	112	82	103
35						86	107
40	86	84	122	84		87	110
45					124	89	108
50	86	85	120	85		87	
55					126	87	
60	80	82				87	
70	78	78					
75					124		
80	78	76					
85		74					
90	72	76			124		

The injection of 2 milligrams (1/33 grain) of atropine subcutaneously produced in ten to fifteen minutes in all the subjects a preliminary period of slowing; this was followed by an increase in the pulse-rate. The increase was very marked (13 to 30 beats per minute) and commenced twenty minutes after the injection of the atropine. (Figure 57). In one case, an increase of thirty beats per minute was still present after ninety minutes. (Table XII.)

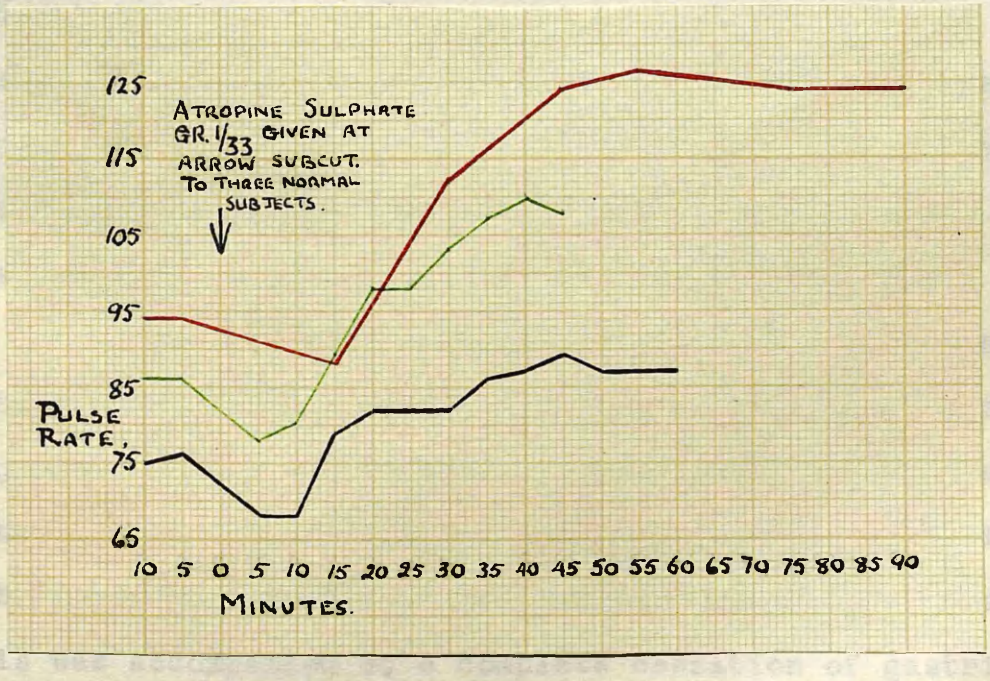


Figure 57.

The effect of atropine sulphate on the pulse-rate can be summarised as follows:-

1. In small doses the pulse is slowed.
2. In large doses after initial slowing, the pulse is quickened.
3. Intermediate doses, 0.6 - 1 mg. (1/100 - 1/60 gr.) do not produce marked tachycardia, but preliminary slowing of the pulse is usually present.

(e) Summation Effect of Atropine:

Danielopolu(1930) noted that in gastric atony 0.5 mg. of atropine produced an improvement in tonus; a repetition of the dose caused less excitation and a third dose actually caused inhibition. In this investigation, a normal person was given, during a phase of hunger contractions, a first injection of 0.1 mg. of atropine intravenously; thirty minutes later the dose was repeated.

The first injection produced a fall in pulse-rate of 10 beats per minute within five minutes of the injection and increased the size and number of the hunger contractions. Following the second injection, the pulse-rate increased, rising 17 beats per minute in five minutes. This was accompanied by a complete cessation of gastric movements. (Figure 58).

Method A.

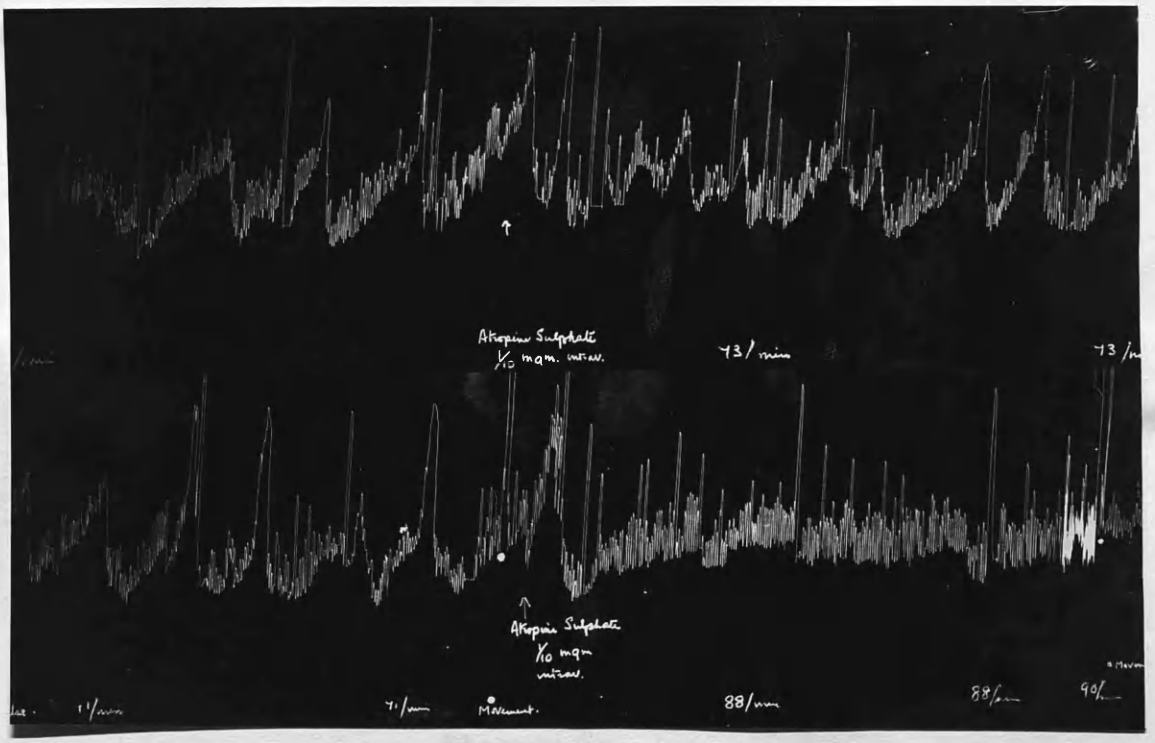


Figure 58.
In Tracing 1, Atropine Sulphate 1/10 mg. intravenously given at arrow.
In Tracing 2, the same dose repeated at arrow.

In a second subject, a first injection of 0.1 mg. atropine intravenously markedly increased the frequency and size of the hunger contractions while the pulse-rate was diminished by 4 beats per minute in five minutes. The same dose, twenty minutes later, caused a complete cessation of contractions and an increase of 7 beats per minute in the

pulse-rate in five minutes. In a third normal subject, a first injection of 0.1 mg. given in a period of tonus change, was followed in ten minutes by the onset of typical hunger contractions. A second injection of 0.05 mg. twenty minutes later caused a marked slowing of the contractions. (Figure 59).

Method B.

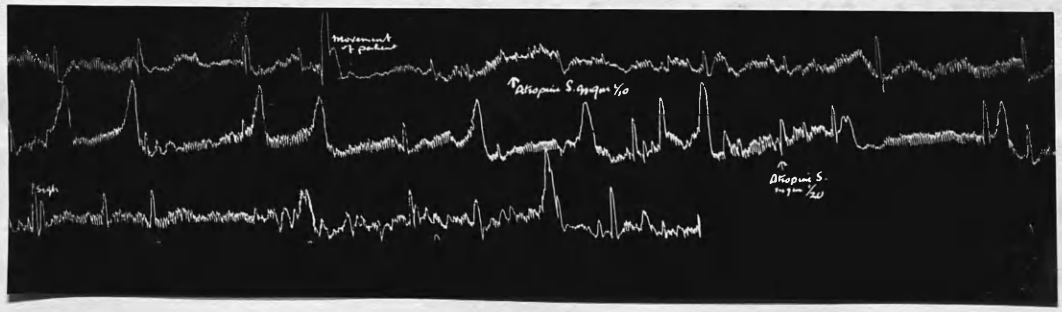


Figure 59.

Atropine Sulphate 1/10 mg. intravenously given at arrow in Tracing 1, and Atropine Sulphate 1/20 mg. at arrow in Tracing 2.

As a control, two of the above normal subjects were given 0.2 mg. of atropine sulphate intravenously during a period of gastric contractions. The gastric motility was unaltered for ten and fifteen minutes respectively and then an increase in frequency and in amplitude occurred in both cases. After the injection, the

pulse-rate was slowed by 3 beats per minute in five minutes in the first patient, and unaltered in the second.

From these observations it appears that if a small dose of atropine is administered intravenously, a second small dose given within thirty minutes of the first, produces the effect usually caused by a much greater dose, i.e. cessation of contractions and quickening of pulse-rate. In these cases 0.05 mg. of atropine given after 0.1 mg. will cause the effect usually seen after 0.6 mg. intravenously. When the two small doses are given together as in the controls (0.2 mg.) the effect characteristic of that range of dosage is seen, namely an increase in the frequency and amplitude of the contractions while if any action on the pulse-rate is produced it is slowing. This suggests that clinically repeated small doses of atropine should have a much stronger action than one single large dose.

(f) Mode of Action of Atropine:

Regarding the effect of atropine on gastric motility and on the pulse-rate, it may be stated first that this is relatively constant. Any dosage from 0.05 mg. to 0.3 mg.(1/1200-1/200 gr.) intravenously produces a slowing of the pulse and an increase of gastric motility. In this range when subcutaneous administration is employed 0.6 mg.

(1/100 grain) is the maximum. This is due to the fact that intravenous injection brings the whole of the drug to the tissues immediately whereas absorption after subcutaneous injection is slower and does not produce as large a contraction. For practical purposes 0.3 mg. (1/200 grain) by intravenous injection is approximately equal to 0.6 mg. (1/100 grain) by the subcutaneous route.

When dosage is increased to the range 0.6 - 1 mg. (1/100 - 1/60 gr.) subcutaneously, it is impossible to predict what the effect of the drug will be. In most cases no sedative effect is exerted on gastric motility; slight excitation is common and the pulse-rate is frequently slowed.

Subcutaneous injection of any amount exceeding 1 mg. always produces a complete cessation of gastric motility and in most cases preliminary slowing of the pulse followed by quickening.

The contrast between the effects of small and large doses of atropine probably explains the absence of preliminary slowing of the pulse after intravenous injections. Relatively slow absorption after subcutaneous injection reproduces the effects of giving a very small dose; this results in a short period of bradycardia. Later, when a larger quantity of the drug enters the circulation tachycardia supervenes.

The vagus nerve acts as an inhibitor to the heart, and it is generally recognised that stimulation of the vagus causes a slowing of the heart. Paralysis of the vagus is thus associated with a quickening of the pulse-rate. The vagus action on the stomach is more complicated. Stimulation of the nerve is supposed to cause active peristalsis. Paralysis of the vagus results in a sedative effect on the stomach.

My own observations suggest that small doses of atropine stimulate the parasympathetic nerve supply to the heart and stomach, that medium doses produce an intermediate stage of balance, and that large doses paralyse the parasympathetic. If this hypothesis is correct, then it explains the change in action, as it affects the pulse-rate as well as the gastric motility.

Cannon(1911) states that splanchnic section produces no change in the normal movement of the stomach, and it therefore appears unlikely that small doses of atropine paralyse the sympathetic. In addition it is doubtful if paralysis of the sympathetic would produce slowing of the heart, as Wright(1940) states that bilateral excision of the stellate ganglia in man, which cuts off most of the sympathetic supply of the heart, has little effect on its rate at rest.

Bastedo (1932) remarks on the slowing of the heart with small therapeutic doses, and attributes this action to stimulation of the vagus centre. He quotes Heidenkamp who suggested this explanation because the phenomenon is abolished in ether anaesthesia and after section of the vagi. Bastedo also states that only small doses have this effect and he describes the investigations of Rudolf and Bulmer. These workers gave fifty patients 1/100 gr. of atropine sulphate by mouth and obtained a prolonged reduction in pulse-rate of 8-10 beats per minute in a high proportion. Clark (1940) finds that 0.5 mg. (1/120 gr.) subcutaneously causes an initial slowing due to central stimulation, followed in about twenty minutes by acceleration, the drug having antagonised the action of acetylcholine on the pace maker of the heart. He states that one milligram (1/60 gr.) causes acceleration of the pulse and dilatation of the pupil.

The results of my own observations on the pulse-rate show that the usual action of small doses of atropine (up to and including a single dose of 0.6 mg. (1/100 gr. subcutaneously) is to slow the pulse. This appears due to a stimulation of the parasympathetic nerves which may be central or peripheral.

Meyer and Gottlieb (1926) state that the greater

the preceding stimulation of the vagus nerve-endings, (e.g. after pilocarpine or choline) the more marked the effect which the atropine produces. This last statement may explain why Quigley,(1937) obtained complete inhibition of the cardiac portion, middle part and pyloric division of the stomach after 0.65 mg. of atropine sulphate subcutaneously. He found also that 0.32 mg. atropine caused marked depression of gastric activity. This worker used insulin to produce hypermotility, and his results may be explained by the fact that atropine works better when there has been a preceding period of stimulation.

Danielopolu(1930) considers that small doses of atropine stimulate the parasympathetic supply to the gastro-intestinal tract as well as the heart. Sachs(1936) states that atropine is amphotropic but predominantly vagotropic. He finds that in small doses it stimulates and in big doses it inhibits both systems, and holds that the action on the parasympathetic is so much stronger that one can neglect the sympathetic action especially if ordinary doses are used.

Bastedo,(1936) in a more recent article, summarising the uses and mode of action of atropine, states that cutting the vagi represents the extreme effect of atropine. He quotes McCrea and McDonald(1929) who gave atropine

intravenously to cats and found that atropine arrested the movements of the stomach and eliminated both vagus and splanchnic control. Bastedo(1936) himself finds that in man, even the most severe grades of hypertonus, hyperperistalsis, and spasm in the body of the stomach, yield to large doses of atropine. His minimum effective dose is one milligram of atropine sulphate by subcutaneous injection, and he concludes that in single maximal doses, atropine hypodermically, may have a limited value in reducing spasm and secretion, but in the doses usually employed or permissible for continued treatment, atropine and belladonna are practically without effect on the motor or the secretory functions of the stomach.

My own findings seem to justify the conclusion that in order to produce quiescence of the empty stomach or a quickening of the pulse, the minimum effective dose by subcutaneous injection is atropine gr. 1/50. In one case (Case III.) shown in Table IV., the atropine caused a slowing of the pulse accompanied by a cessation of gastric contractions. These actions cannot be explained by either a stimulation or a paralysis of the sympathetic or parasympathetic system. Later it will be shown that .4 mg. (1/150 gr.) of atropine given after .5 mg. (1/120 gr.) of Prostigmin had the same effect.

The only conclusion, compatible with existing

theories of sympathetic and parasympathetic action, seems to be that small doses stimulate the parasympathetic system, and that large doses have the opposite effect. Thus in the cases mentioned above, a dual action occurred, the drug having a parasympathetic stimulant effect on the heart accompanied by a paralysis of the vagus nerve-supply to the stomach.

When the summation effect of atropine is recalled, i.e. the fact that a small dose intravenously produces the usual stimulant effect on gastric motility with a slowing of the pulse, while a second small dose has the reverse and opposite effect, it can be postulated that the first dose sensitized the parasympathetic system in some way. Thus the second small dose produced the effect usually found with much larger doses. A pure cumulative effect is disproved because when the sum of the two small doses is given at one time intravenously a small-dosage action is produced. The first atropine injection must in some way alter the response of nerve-endings to the second administration of atropine.

SUMMARY

Most workers believe that atropine sulphate paralyses the parasympathetic nerve-endings. Danielopolu (1930) however, suggested that small doses (0.05 mg.) of atropine

caused an increase in the tone and amplitude of gastric contractions accompanied by a slowing of the pulse. In my own investigation doses from 0.05 - 0.3 mg. intravenously produced an excitatory effect on gastric motility and caused slowing of the pulse. Intravenous administration of 0.4 - 1 mg. was followed by cessation of gastric motility and in most cases by quickening of the pulse. Atropine sulphate 0.6 mg. subcutaneously had a variable effect on the movements of the stomach and this was accompanied by slowing of the pulse. The effect on normal subjects and in patients suffering from peptic ulceration was similar. Hypodermic injections of 1.2 - 2 mg. caused in all cases a cessation of gastric motility and preliminary slowing of the pulse followed by a marked increase. The action on the pulse-rate ran parallel with the effect on stomach movements. A summation effect of atropine sulphate was demonstrated. It is postulated that small doses of atropine stimulate the parasympathetic system, that medium doses produce an intermediate stage of balance and that large doses paralyse the parasympathetic. It is further suggested that the summation effect is due to the first small dose rendering the parasympathetic system more susceptible to atropine. The second injection then produces the effect usually seen with a large dose.

S E C T I O N 3.

NOTE ON ACTION OF TRASENTIN AND SYNTROPAN

Certain synthetic substances have been used with a view to retaining the anti-spasmodic action of atropine while excluding the other side-actions, e.g. palpitation.

Among these, Trasentin and Syntropan are substances which have been tried. The effect of Trasentin, or diphenylacetyldiethylaminoethanol ester, has been studied on animals by Meier (1936) and Necheles, Neuwelt, Steiner and Motel, (1939) who demonstrated an anti-spasmodic action. Graham and Lazarus (1940) reviewed the literature and compared the drug with a newer derivative, Trasentin-6-H. Trasentin itself has been recommended for use in renal colic, and Crassousi, (1937) Einhorn, (1938) Spier et alii (1939) found it useful in spasmodic conditions of the gall-bladder and gastro-intestinal tract. The dose recommended is ½ to 1 ampoule daily by subcutaneous or intramuscular injection.

In my own investigation, an injection of 3 c.c. of Trasentin was given intramuscularly to two patients with normal stomachs.

Case I. Fifteen minutes after the injection, complete cessation of gastric contractions occurred and this quiescent phase lasted for thirty-five minutes. (Figure 60).

Method A.

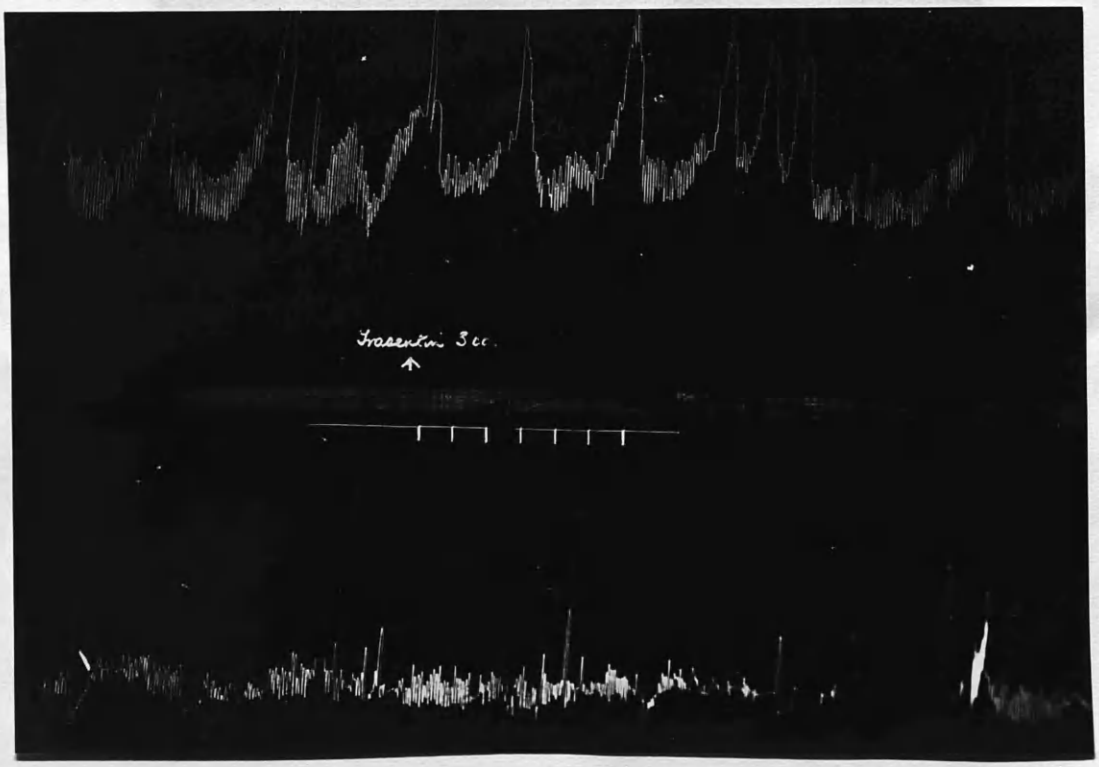


Figure 60.
Trasentin 3 c.c. given at arrow in Tracing 1.

Case II. Four minutes after administration the gastric contractions slowed from four contractions in five minutes to two contractions in the same period. No cessation of contractions occurred. This slowed phase lasted for thirty-five minutes. (Figure 61).

Method A.

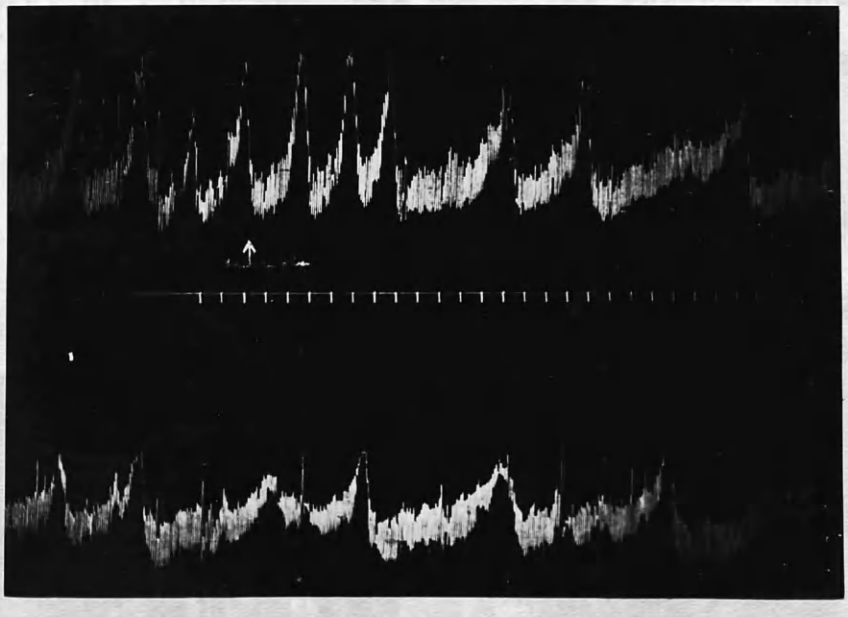


Figure 61.

Trasentin 3 c.c. given at arrow in Tracing 1.

In both cases no alteration was noted in the pulse-rate.

Syntropan is the 3-diethylamino-2: 2 dimethyl-propanol ester of tropic acid and is given in doses of 1 c.c. by intramuscular injection or orally as tablets.

Clark, Shires, Campbell and Welch (1939) compared the doses of atropine and syntropan that were required to produce the same degree of depression in the intestine of dogs; they found that atropine was one

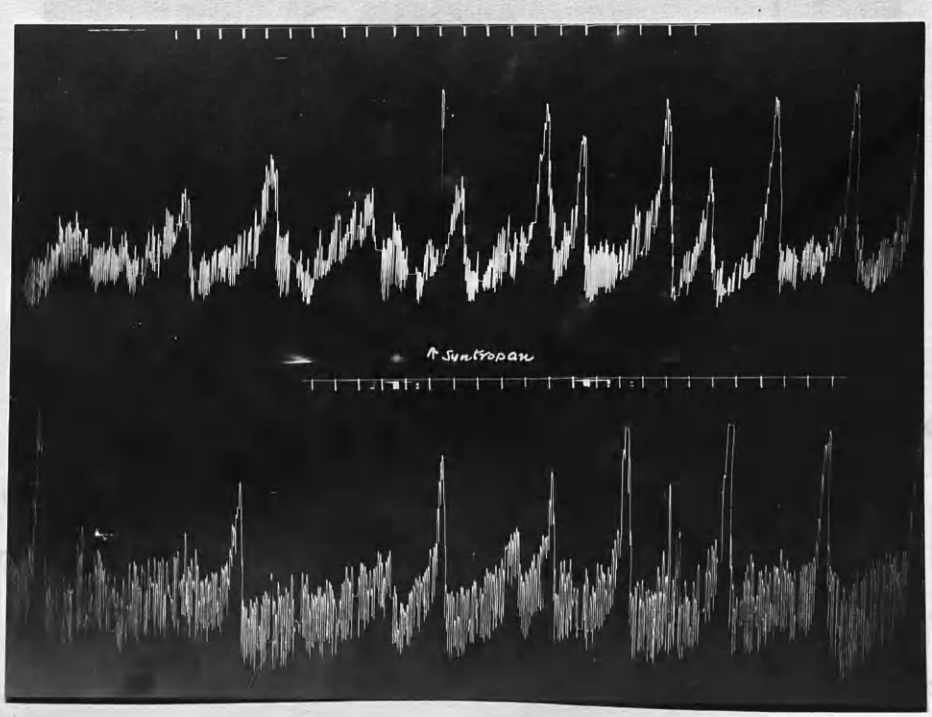
hundred times more powerful than syntropan.

In this investigation three normal subjects were given 2.5 - 3 c.c. of Syntropan intramuscularly.

Case I. Following the intramuscular injection of 2.5 c.c. of Syntropan, the number of gastric contractions was reduced from three in five and a half minutes to two in the same time. (Figure 62).

Method A.

1.



2.

Figure 62.

2.5 c.c. Syntropan given at arrow in Tracing 1.

Case II. Seventeen minutes after the intramuscular injection of 3 c.c. of Syntropan, a phase of increased contractions occurred; this was followed by a period of cessation which lasted for eight minutes and then the contractions were resumed.

Case III. Complete cessation of gastric contractions occurred two minutes after the injection, and quiescence lasted forty-five minutes. (Figure 63).

Method A.

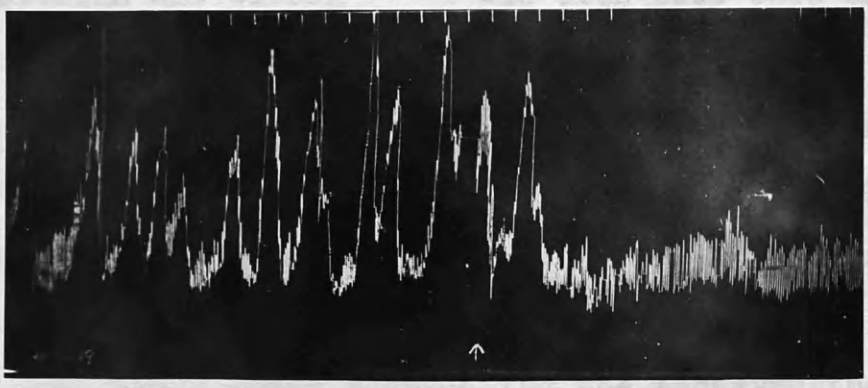


Figure 63.

Syntropan 3 c.c. given at arrow.

The pulse-rate was unaltered in Cases I. and II., and quickened by 6 beats per minute after ten minutes in Case III.

From the results shown here, it appears that these two substances have usually mild sedative actions on gastric motility free from any marked effect on the pulse-rate. They appear to be much less powerful than atropine, even when large doses are given.

S E C T I O N 4.

THE ACTION OF CALCIUM

The effect of calcium salts on the gastric motility has been investigated by many workers. Carlson (1916) stated that calcium chloride produced a temporary depression. Dickson and Wilson (1928) who also used this salt found increased peristalsis.

Danielopolu (1930) showed that while smaller doses of the chloride caused a transient increase or inhibition of gastric contractions, larger doses always produced inhibition. Calcium according to this author, was amphotropic, small doses stimulating the parasympathetic system predominantly, large doses the sympathetic system.

Neidhart (1935) found that 5-10 c.c. of 1% calcium chloride intravenously produced a cessation of the movements of the fasting stomach lasting ten to thirty minutes. In the present investigation, 10 c.c. of 10% calcium gluconate solution were given intravenously to seven patients with normal stomachs.

Case I.

The injection of calcium gluconate was given during a period of gastric contractions. Before the administration, six contractions had occurred in a ten minute period. Within ten minutes of the intravenous medication, the contractions had slowed to three per ten minutes and the individual waves were of lower amplitude. The pulse-rate had dropped from 66 beats per minute to 60 beats per minute, five minutes after the injection.

Cases II., III., and IV.

Five to six minutes after the injection of calcium, complete cessation of contractions occurred. The pulse-rate dropped five beats per minute in five minutes in Case II., and 4 beats per minute in ten minutes in Cases III. and IV. (Figure 64).

Method A.

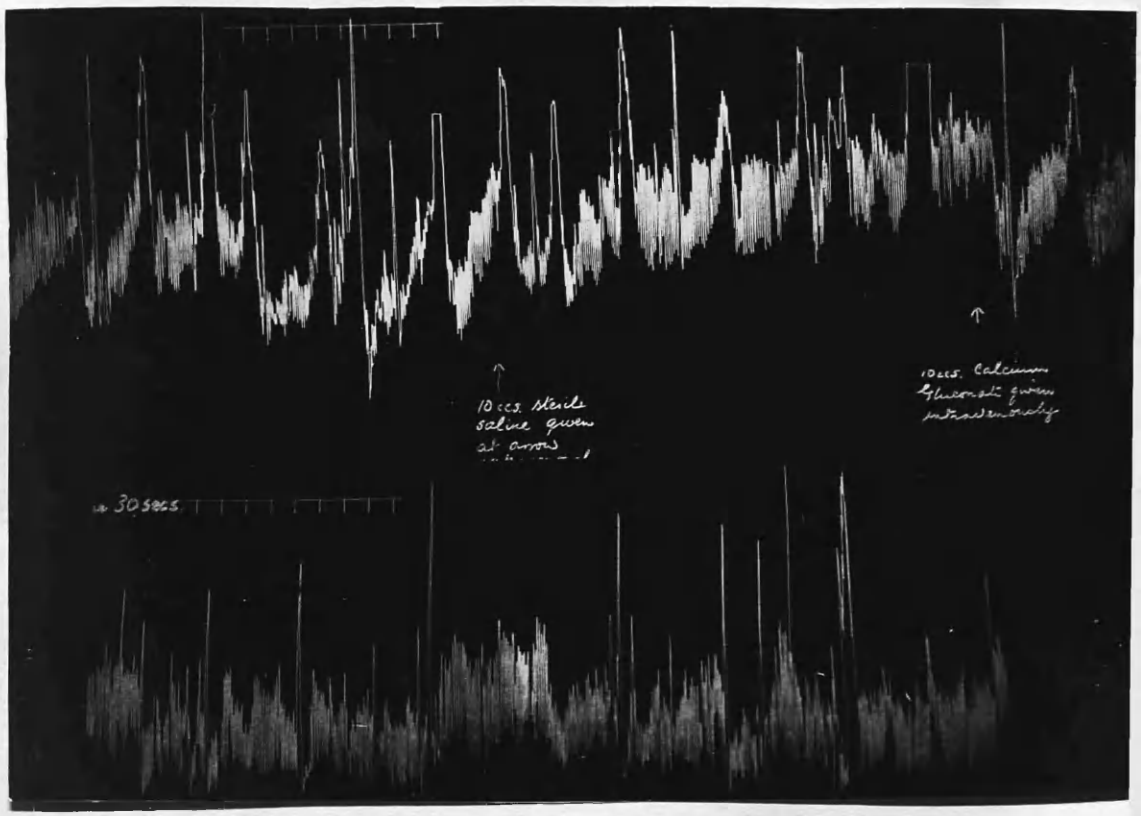


Figure 64.

In Tracing 1, 10 c.c. saline given at first arrow, and 10 c.c. Calcium Gluconate given at second arrow.

Case V.

Cessation of gastric peristalsis was found five minutes after the calcium administration. This quiescent phase lasted for ten minutes and then the contractions were resumed. The pulse-rate slowed, falling three beats per minute in ten minutes.

Case VI.

In a ten minute period before calcium was given, eight contractions occurred. In the same interval after the injection, five waves of lower amplitude were found. Within five minutes of the injection the pulse-rate had dropped six beats per minute.

Case VII.

Contractions continued with approximately the same frequency as before the calcium but with a much lower amplitude. The pulse-rate dropped six beats per minute in ten minutes after the calcium administration.

From these results, it is concluded that calcium in moderate dosage produces (a) a sedative effect on gastric contractions and (b) a slowing of the pulse-rate.

The following observations were made in order to determine whether the response to atropine is affected by the previous administration of calcium gluconate. The results are shown in Figure 65 and Table XIII.

Method B.

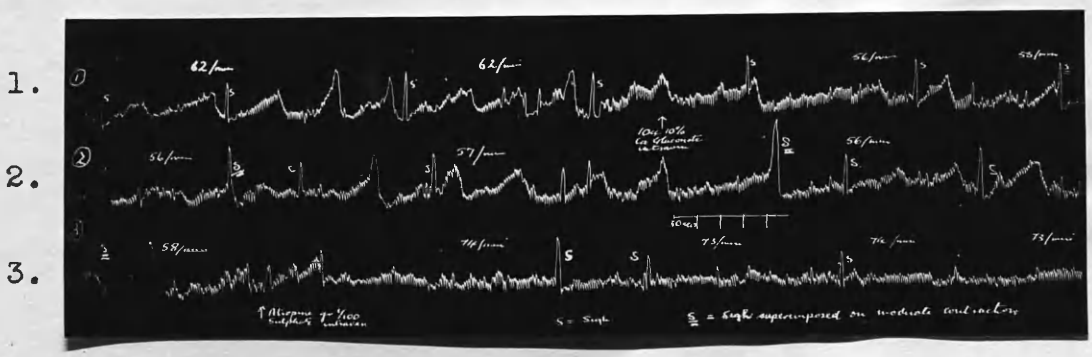


Figure 65.
10 c.c. Calcium Gluconate given at arrow in Tracing 1, and gr.1/100 Atropine Sulphate given at arrow in Tracing 3.

T A B L E XIII.

Calcium and Atropine

C = 10 c.c. Calcium Gluconate. A = 0.6 mg. (1/100 gr.) Atropine Sulphate, both given intravenously.

Drugs Given	Action on Pulse	Action on Gastric Motility
Atrop.Sulph. 40 min. after calc. gluc.	C - in 5 mins. a slowing of 6 beats/minute. A - in 5 mins. an increase of 10 beats/min.	C - given during hunger contractions - slight sedative effect. A - complete cessation.

It will be seen that while both these substances have the same action on the stomach, i.e. sedative, different effects are produced by these drugs on the pulse-rate, the calcium slowing the pulse while the atropine quickens it.

In a further series of experiments, calcium gluconate was given and later a small excitatory dose of atropine. (Table XIV.)

T A B L E XIV.

C = 10 c.c. Calcium Gluconate. A = 0.1 mg. Atropine Sulphate, both given intravenously.

Case	Drugs Given	Effect on Pulse	Effect on Gastric Motility
1.	Atropine Sulphate given 25 minutes after Calcium Gluconate.	C - in 10 mins. a slowing of 4 beats/ min. A - in 5 mins. a slowing of 4 beats/ min.	C - cessation of contractions in five mins. A - one very powerful contraction immediately after the injection then quiescence for 9 mins. followed by the onset of very powerful and frequent contractions.
2.	Atropine Sulphate given 20 minutes after Calcium Gluconate.	C - in 10 mins. a slowing of 6 beats/ min. A - in 5 mins. a slowing of 6 beats/ min.	C - contractions continued of same frequency but much lower amplitude. A - two very powerful contractions immediately after the injection, followed by quiescence for 10 mins. Then the contractions became more powerful and more frequent.
3.	Atropine Sulphate given 15 minutes after Calcium Gluconate.	C - in 10 mins. a slowing of 4 beats/ min. A - in 5 mins. a slowing of 4 beats/ min.	C - cessation of contractions in 5 mins. A - 10 mins. after the injection small gastric contractions started.

These results show that the calcium prevented the usual motor action on the stomach of a small dose of atropine. This motor effect of atropine seems only to have been held in check, for in every case, after a period of about ten minutes, contractions started again and in two of the subjects these were even more powerful than the movements recorded before the administration of calcium.

In these experiments the drugs had the same effect on the heart but different actions on the stomach. Slowing of the pulse occurred after injection of either; on the stomach however the calcium maintained its usual sedative effect and the small dose of atropine had its motor action modified as would be expected by the premedication with calcium.

Rogen(1940) explains the effect of calcium on the heart-rate as a stimulating action on the vagus, and as far as can be judged from the pulse-rate, my own findings are consistent with his views.

Sachs(1936) states that calcium stimulates the sympathetic system, and again judged by my own work on gastric motility, this explanation appears to be correct.

To correlate these two actions, it appears reasonable to assume that a substance can stimulate the sympathetic fibres to one organ, and the parasympathetic

to another. In this case, the dose of calcium that excites the sympathetic nerve supply to the stomach results in stimulation of the parasympathetic nerve fibres to the heart. The possibility of the same stimulus having a sympathetic action on one organ and a parasympathetic effect on another has been previously mentioned. Danielopolu(1930) explains the oculo-gastric reflex by this theory.

It is possible to postulate the alternative theory that calcium stimulates the vagus supply to the heart and at the same time paralyses the parasympathetic nerve fibres to the stomach. It will be recalled the atropine gr. 1/100 intravenously was found to have a similar effect in one subject. Calcium, however, is not a very powerful inhibitor of gastric motility as compared with atropine, and it seems improbable that there is any question of paralysis of the vagus nerve endings.

S E C T I O N 5.

THE ACTION OF PROSTIGMIN

Aeschlimann and Reinert (1931) showed that a synthetic analogue of physostigmine, the dimethyl-carbamic ester of 3 -oxphenyl-trimethyl-ammonium-methyl sulphate, had pharmacological properties similar to those of physostigmine. This substance, known as prostigmin, stimulates intestinal peristalsis but has less effect on the heart and circulation than physostigmine. Ammon (1934) showed that prostigmin inhibited choline esterase as does physostigmine. Thus the result of its administration is due mainly to the potentiation of acetyl-choline effects occurring normally in the body. This would roughly correspond to stimulation of the parasympathetic system. Prostigmin has been found by Weigand, (1931) Leiner, (1931) Kottlers, (1932) Begg, (1937) Harger and Wilkey, (1938) and by Carmichael, Fraser, McKelvey and Wilkie, (1934) to have a beneficial effect on post-operative atony of the bowel. In addition, this drug has been used with great success by Walker (1934, 1935) and others in the treatment of myasthenia gravis. Fraser, (1938) in a recent paper, gives a complete account of this drug. In this investigation,

the action of prostigmin alone, and prostigmin with atropine, has been studied on the gastric motility.

In the first instance, the effect of prostigmin alone by intravenous injection was determined on gastric motility and on the pulse-rate. The same result was obtained in each case. (Table XV.)

T A B L E XV.

The Action of Prostigmin

Prostigmin - 0.5 mg. intravenously in all cases.

Case	Pulse-rate	Gastric Motility
1.	Maximum slowing within 25 mins. of 9 beats/min.	Increase of amplitude, strength and frequency of contractions within 10 mins. MOTOR EFFECT.
2.	Maximum slowing within 15 mins. of 9 beats/min.	Marked increase in amplitude and strength of contractions in 7 mins. MOTOR EFFECT.
3.	Maximum slowing within 10 mins. of 8 beats/min.	Marked increase in amplitude and strength of contractions in 6 mins. MOTOR EFFECT.
4.	Maximum slowing within 10 mins. of 8 beats/min.	Marked increase in amplitude and strength of contractions in 10 mins. MOTOR EFFECT.
5.	Maximum slowing within 15 mins. of 11 beats/min.	Marked increase in frequency, amplitude and strength of contractions in 4 mins. until tetanic contractions occurred. MOTOR EFFECT.
6.	Maximum slowing within 15 mins. of 13 beats/min.	Marked increase in frequency and amplitude of contractions in 12 mins. MOTOR EFFECT.
7.	Maximum slowing within 10 mins. of 21 beats/min.	Marked increase in frequency and amplitude of contractions in 5 mins. MOTOR EFFECT.
8.	Maximum slowing within 20 mins. of 6 beats/min.	Marked increase in 9 mins. in amplitude and frequency of contractions. MOTOR EFFECT.

It is evident that prostigmin produces marked slowing of the pulse-rate accompanied by increased activity of the stomach. A typical tracing is shown in Figure 66.

Method B.

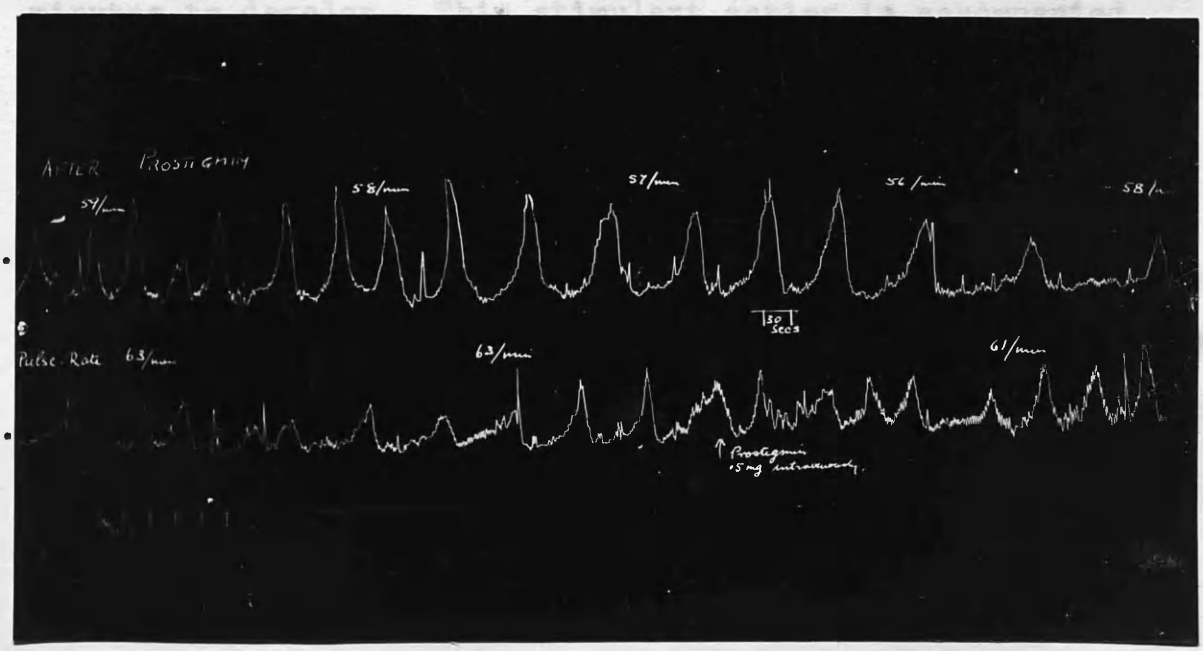


Figure 66.
Prostigmin 0.5 mg. given intravenously at arrow in Tracing 1.

In every case the slowing of the pulse started within five minutes of the injection; the maximum fall in

pulse-rate was reached in ten to twenty-five minutes after the injection. The action on the gastric motility occurs in four to twelve minutes after giving the prostigmin. The striking uniformity of action in this series leaves no doubt as to the effect of the prostigmin.

It can be concluded from the Table and tracing, that prostigmin given intravenously in a dose of 0.5 mg. has a constant excitor effect which takes four to twelve minutes to develop. This stimulant action is accompanied by slowing of the pulse varying from six to twenty-one beats per minute.

THE ACTION OF PROSTIGMIN AND ATROPINE

Prostigmin has been shown to have an excitatory effect on gastric motility and to slow the pulse. In the following investigation atropine was given after prostigmin to see if any change in the atropine action was produced. Two subjects were given prostigmin 0.5 mg. intravenously and twenty minutes later atropine sulphate 0.4 mg. (1/150 gr.) by the same route. It has been shown that sometimes a period of twelve minutes elapses before the action of prostigmin appears, hence injections were spaced at intervals of not less than twelve minutes.

T A B L E XVI.

Action of Prostigmin and Atropine on Gastric Motility and Pulse-rate

Drugs given intravenously: P = 0.5 mg. Prostigmin.
A = 0.4 mg.(1/150 gr.)Atropine.

P.	A (After 20 mins.)	Slowing in 15 mins. of 10 beats/min. after P. Slowing 10 beats/ min. more after A.	P - Motor effect ++ A - Immediate sedative effect.
P.	A (After 20 mins.)	Slowing in 15 mins. of 13 beats/min. after P. Slowing of 13 beats/ min. more after A.	P - Motor effect ++ A - Sedative effect in 20 mins. (had to overcome P.)

Method B.

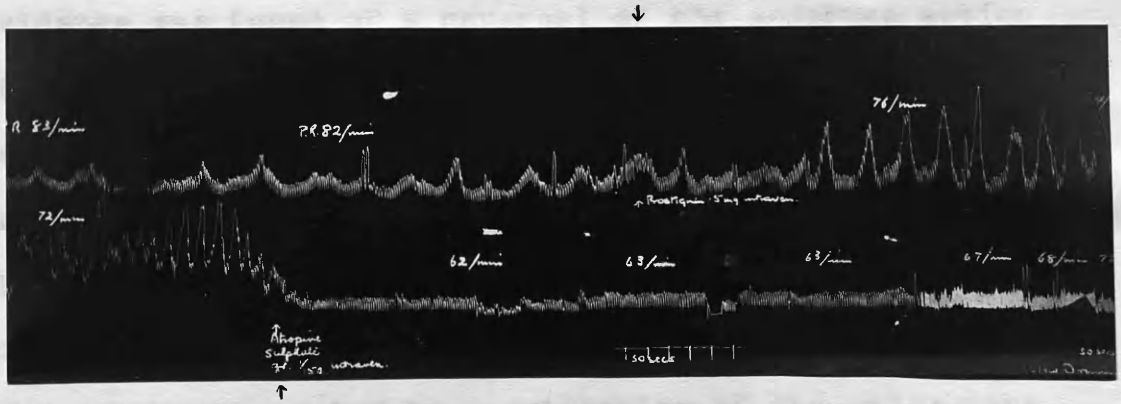


Figure 67.

At arrow in Tracing 1, 0.5 mg. prostigmin given intravenously; at arrow in Tracing 2, atropine sulphate gr. 1/150 given by the same route.

Method B.

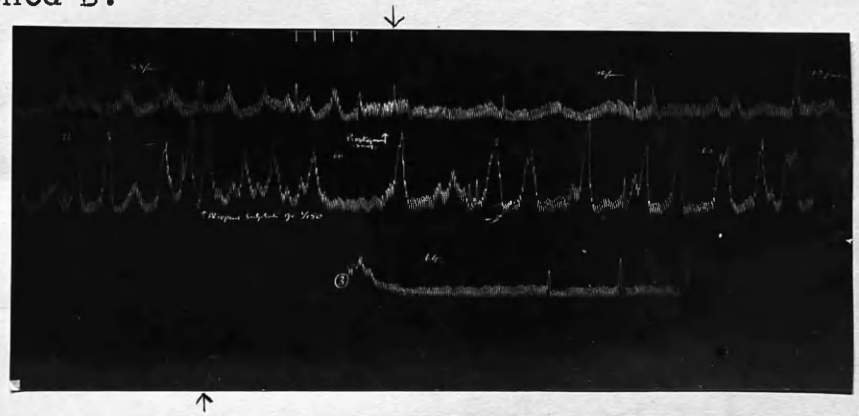


Figure 68.

At arrow in Tracing 1, 0.5 mg. prostigmin given intravenously; at arrow in Tracing 2, atropine sulphate gr. 1/150 given intravenously.

Table XVI. and Figures 67 and 68 show that prostigmin has its usual excitatory action on the stomach movements and that atropine exerts a sedative effect. No evidence was found of a reversal of the sedative action of atropine to a motor one. The effect on the pulse-rate was in both cases slowing, after the prostigmin injection and again after the atropine administration. It has been shown previously that atropine in this dose without prostigmin premedication has a sedative action on the gastric movements accompanied by a quickening of the pulse-rate. The slowing effect which is then produced by this dose of

atropine is unusual. A possible explanation is that atropine in a dose of 0.4 mg. intravenously is on the border zone of atropine action and the strong parasympathicomimetic effect of the prostigmin has altered the action of the atropine on the heart-rate, changing it to vagal stimulation. In this connection Meyer and Gottlieb(1926) found that the higher the preceding state of tonus of the stomach the more pronounced was the action of atropine. Here then the usual sedative effect is maintained owing to the strong contractions and high tonus produced by the prostigmin. Whatever the explanation, it is again evident that a drug (in this instance atropine) may have a parasympathetic stimulant action on one organ and a parasympathetic paralysant effect on another. This example supports the theory of atropine action outlined above.

It has been shown that prostigmin has a stimulant effect on gastric motility and that atropine given after the prostigmin exercises its usual sedative action.

These conclusions are in direct contrast to the findings of Veach, Lauer and James.(1938) These authors stated that (1) prostigmin is usually inhibitory to the stomach, (2) the inhibitory action of atropine on the human stomach is changed into excitation by prostigmin, (3) atropine increases the infrequent motor effect to a

marked motor action, and (4) atropine and prostigmin act on the same structure probably the receptive substance of Langley. The prostigmin was given by these authors intravenously in dosage of 0.5 to 2 mg., and the usual dose of atropine was 0.4 to 0.8 mg. Before attempting to find any cause for these completely opposing views, certain experiments were performed in a further examination of the other conclusions reached by these writers.

Their third conclusion was that atropine increases the infrequent gastric motor effect of prostigmin or changes its inhibitory effect to a marked motor action. To verify this statement, atropine gr. 1/60 was given intravenously to a healthy patient and fifteen minutes later 0.5 mg. prostigmin was administered by the same route. The atropine injection given during gastric contractions produced an immediate cessation of movements, with a quickening of the pulse-rate of twenty-eight beats per minute in five minutes. The subsequent injection of prostigmin caused no activity, but a fall in the pulse-rate occurred thirty minutes after the prostigmin until it was sixteen beats per minute slower. (Figure 69). The dose of atropine given was such that the parasympathetic nerve endings would be completely paralysed and the prostigmin would thus be unable to produce its usual motor action, due to lack

of response to parasympathetic stimulation. This experiment therefore provided no support for the theories of Veach, Lauer and James.

Method B.

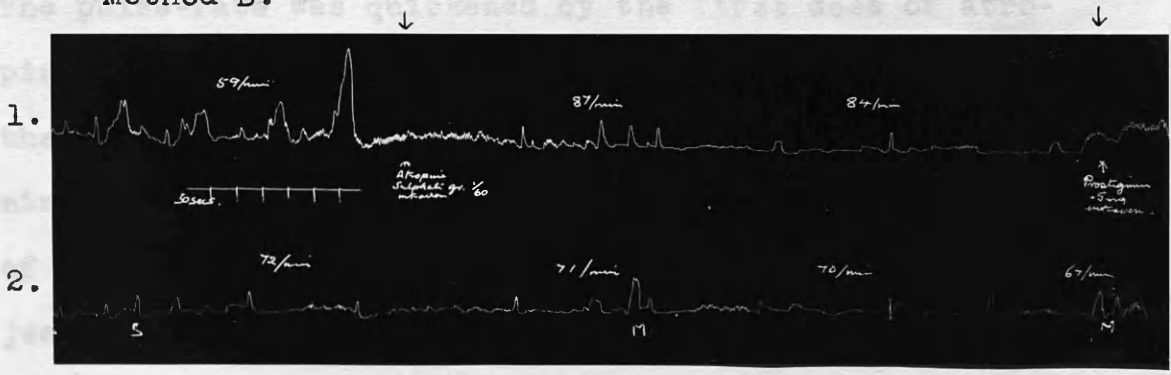


Figure 69.

In Tracing 1, Atropine Sulphate gr. 1/60 given at first arrow.
Prostigmin 0.5 mg. given at second arrow.

It may be objected that the dose of atropine given in my experiment was unduly large. Further observations were therefore made.

As seen in the Tracing (Figure 70), a normal patient was given atropine gr. 1/100 intravenously, prostigmin 0.5 mg. twenty minutes later, and lastly

atropine gr. 1/100 thirty minutes after the prostigmin. The results on the gastric motility can be summarised as follows:-

(a) the first dose of atropine given during a phase of gastric contractions produced the usual sedative effect,

(b) the prostigmin caused motor activity, and

(c) the final injection of atropine had a sedative effect.

The pulse-rate was quickened by the first dose of atropine, slowed by the prostigmin and again quickened by the second dose of atropine. The effect of the prostigmin was in no way altered by the previous administration of atropine. Furthermore, the action of the second injection of atropine was not changed by the prostigmin. No evidence of reversal of action was found.

Method B.

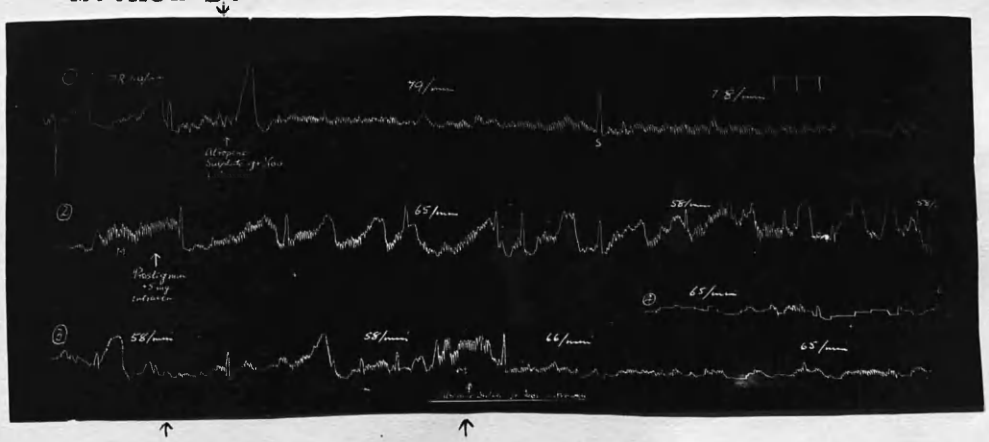


Figure 70.

Atropine Sulphate gr. 1/100 given intravenously in Tracing 1, prostigmin 0.5 mg. given intravenously in Tracing 2 and atropine gr.1/100 given by the same route in Tracing 3.

It is apparent that there was no agreement with the tracings of Veach, Lauer and James. The discussion now centres on why these different results were obtained. Attention is directed first to the type of patient used. In the article in question, a description of the patients investigated was given. The five patients included two who had undergone herniorrhaphy, one with an atonic stomach, a spastic and ptosed colon and cholelithiasis, a fourth with spastic colon and a fifth with cataract, recurrent inguinal hernia, spastic colon and mild arterial hypertension. In my own investigations three patients were used on several occasions. None of them had any pathological condition or had undergone previous surgical treatment and all were enjoying good health at the time of the experiments.

It may well be that the stomach of a patient with intra-abdominal disease or post-operative disturbance reacts in a different way to that of the normal healthy subject, and that the difference is also apparent when the effects of drugs are considered.

Figures 71-74 are taken from the paper by Veach et alii and are typical of their findings on the action of prostigmin and atropine. The table and tracings according to the authors demonstrate (1) that

prostigmin has an inhibitory effect and (2) that previous medication with prostigmin renders the action of atropine motor.

TABLE 1

INTRAVENOUS INJECTIONS	NUMBER	MOTOR	INHIBITORY
		per cent	*per cent*
Prostigmin:			
Before atropine or alone	23	22	78
After atropine	6	100	0
Atropine:			
Before prostigmin	6	0	100
After prostigmin	18	100	0
After motor (reversed) reaction to atropine	3	0	100

Figure 71.

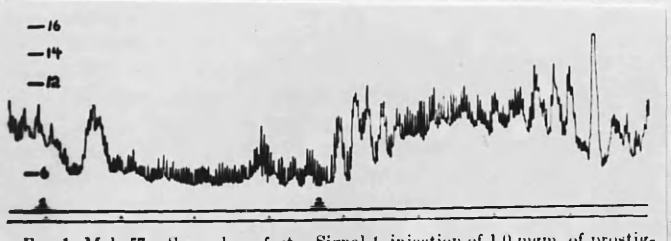


FIG. 1. Male 57. Seven-hour fast. Signal *1*, injection of 1.0 mgm. of prostigmin intravenously. Signal *2*, injection of 0.4 mgm. atropine sulphate. Time 1.87 minutes per unit.

Figure 72.

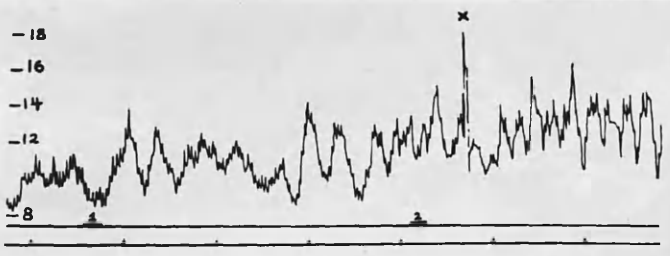


FIG. 3. Male 39. Fourteen-hour fast. Signal *1*, injection of 1.0 mgm. prostigmin. Signal *2*, injection of 0.4 mgm. atropine sulphate. Time 1.87 minutes per unit. Patient cleared throat at *x*.

Figure 73.

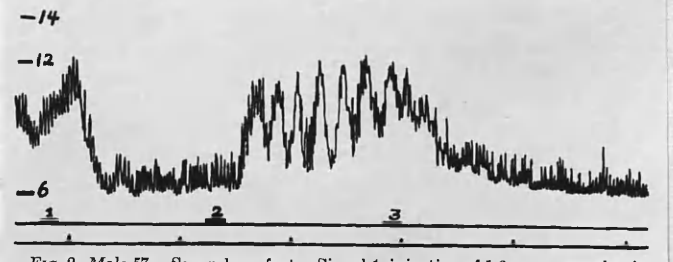


FIG. 2. Male 57. Seven-hour fast. Signal *1*, injection of 1.0 mgm. prostigmin. Signal *2*, injection of 0.4 mgm. atropine sulphate. Signal *3*, injection of 0.4 mgm. atropine sulphate. Time 1.87 minutes per unit.

Figure 74.

On analysing these illustrations two points were noted, (1) the lack of a control period on the tracing before the injection, in which to enable the state of the gastric motility to be judged, (2) the short interval which was allowed to elapse between the injection of the prostigmin and the subsequent administration of atropine. As the tracings show this interval varied from three to seven minutes.

From these observations, I suggest the following alternative reading of the results.

In Tracings 1 and 3, (Figures 72, 73) the prostigmin exerted its usual motor effect but before this action had become manifest, the atropine was given. The dose of atropine was insufficient to control the motor action produced and thus a fallacious conclusion was drawn. It has been noted previously that prostigmin may take four to twelve minutes to induce its motor effect. Similarly, it can be argued that Tracing 2 (Figure 74) actually shows the usual sedative effect of atropine.

The following investigation was made in an attempt to test the explanation outlined above. Prostigmin 0.5 mg. was given intravenously to a normal patient and ten minutes later atropine sulphate 0.65 mg. (1/100 gr.) by the same route. (Figure 75). The prostigmin had no apparent effect on the gastric motility but the atropine

produced a motor action.

Method B.

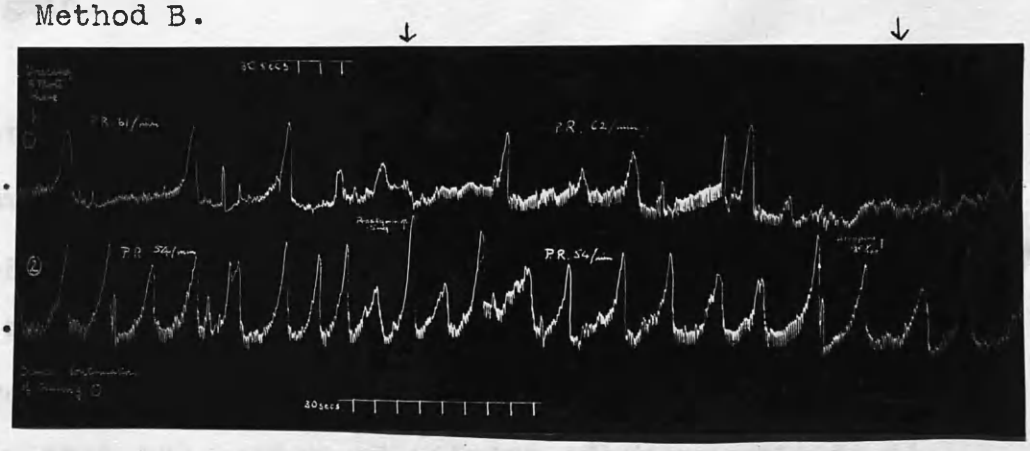


Figure 75.

At first arrow in Tracing 1, 0.5 mg. prostigmin given, at second arrow in Tracing 1, atropine gr. 1/100 given.

The explanation of this phenomenon was provided by the pulse-rate which showed a slowing after the atropine injection by eight beats per minute. It must be emphasised that without previous administration of prostigmin atropine in this dosage intravenously causes a quickening of the pulse as shown elsewhere, and the effect seen here on both gastric motility and pulse-rate is the result of the previous administration of the prostigmin. As demonstrated above, the effect of

prostigmin may take twelve minutes to develop. This seems to indicate that the motor effect following the injection of atropine shortly after the prostigmin is due not to the atropine but to the prostigmin. The atropine in that dosage is unable to overcome the strong excitatory effect of prostigmin.

For the further investigation of this hypothesis, a substance known to have a mild sedative action, namely calcium gluconate, was given intravenously shortly after prostigmin. Calcium gluconate (10 c.c. 10% solution) was given ten minutes after the intravenous injection of 0.5 mg. prostigmin. From the tracing, (Figure 76), it will be seen that the action of calcium after prostigmin is also apparently motor, while the prostigmin appears to have no effect on the gastric peristalsis. Both drugs produce a slowing of the pulse-rate. On analysing this result, it is apparent, as before, that the weak sedative action of calcium is unable to control the strong contractions produced by the prostigmin.

Method B.

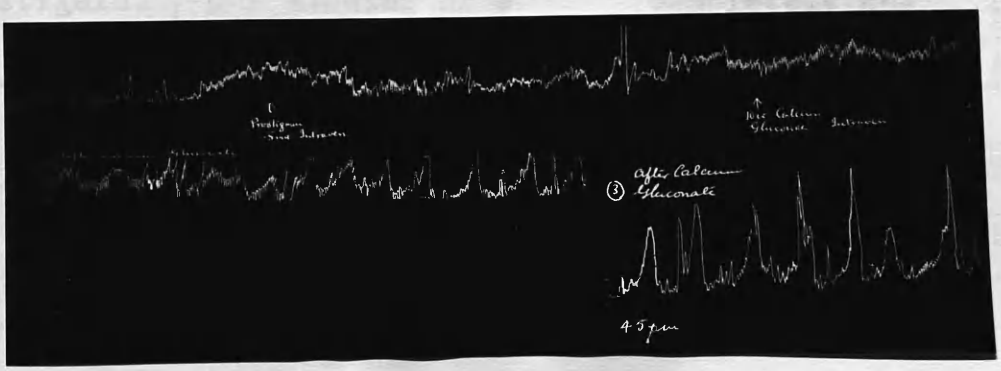


Figure 76.
In Tracing 1, at first arrow 0.5 mg. prostigmin given. At second arrow 10 c.c. Calcium Gluconate given.

Now as with atropine, if some time is allowed to elapse before the calcium is given, in order that the prostigmin may exert its usual action, the calcium will be found to exercise its usual effect as shown in Table XVII. and Figures 77 and 78.

T A B L E XVII.

Action of Prostigmin and Calcium

P = 0.5 mg. Prostigmin intravenously.
C = 10 c.c. of 10% Calcium Gluconate.

Drugs Given	Action on Pulse	Action on Gastric Motility
Calcium Gluconate given 30 mins. after prostigmin.	P - slowing of 6 beats/min. falling to 9 beats/min. in 20 mins. C - slowing of 2 beats/min.	P - Motor effect in 10 mins. C - Complete cessation in 13 mins.
Calcium Gluconate given 25 mins. after prostigmin.	P - slowing of 3 beats/min. in 5 mins. of 6 beats/min. in 15 mins. C - slowing of 3 beats/min.	P - Motor effect in 8 mins. C - Sedative effect unable to overcome completely the motor effect of P.

Method B.

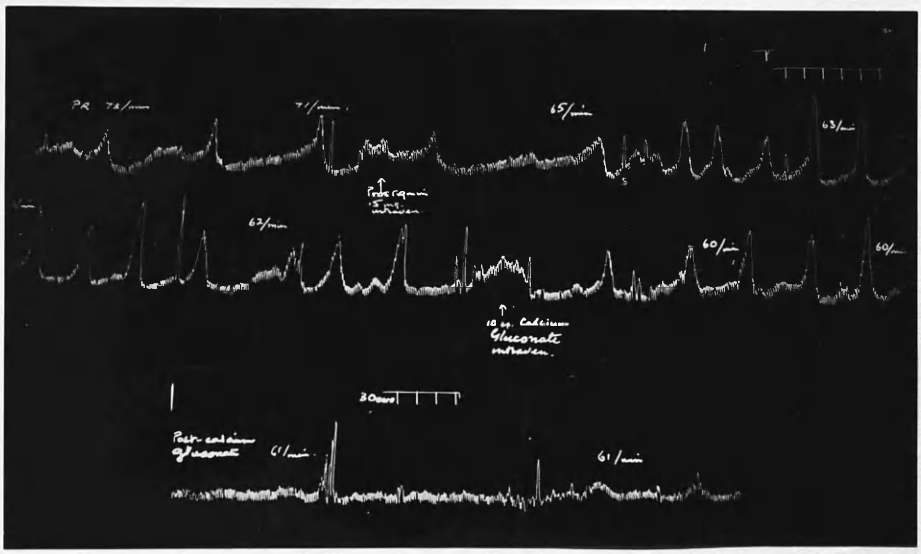


Figure 77.

Prostigmin 0.5 mg. given at arrow in Tracing 1.
10 c.c. Calcium Gluconate given at arrow in Tracing 2.
Both intravenously.

Method B.

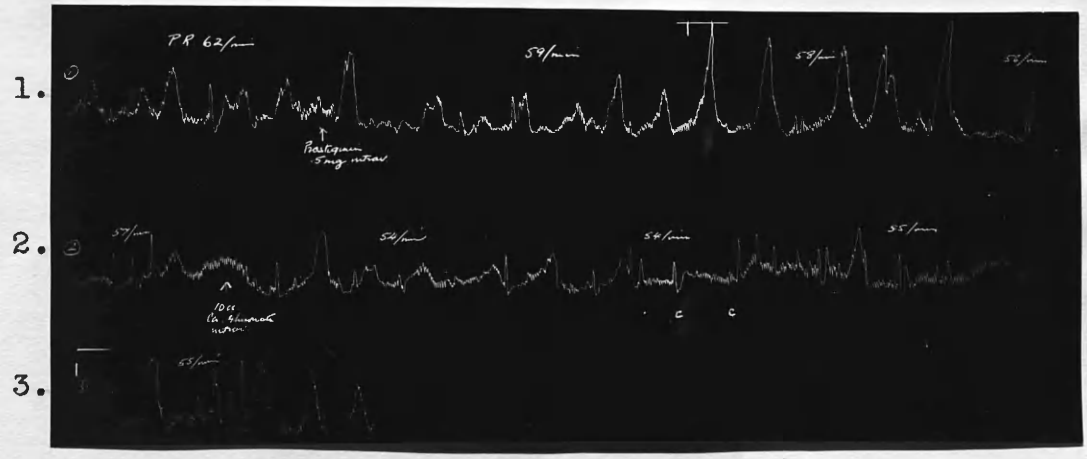


Figure 78.

At arrows, prostigmin 0.5 mg. given in Tracing 1,
Calcium Gluconate 10 c.c. in Tracing 2.

These results show that calcium produces its usual sedative effect, and prostigmin its usual motor action.

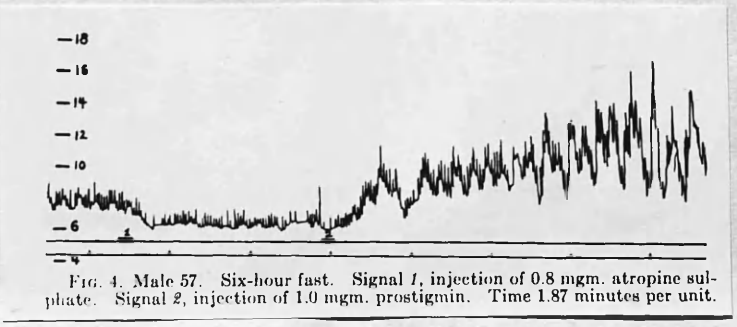


FIG. 4. Male 57. Six-hour fast. Signal *1*, injection of 0.8 mgm. atropine sulphate. Signal *2*, injection of 1.0 mgm. prostigmin. Time 1.87 minutes per unit.

Figure 79.

In the tracing reproduced above (Figure 79) from the paper by Veach et alii, atropine evidently had its usual sedative action; but the dose given was not great enough to prevent the excitor action of prostigmin. As before, calcium gluconate was used to compare the action with that of atropine. 10 c.c. of calcium gluconate, given intravenously before the prostigmin, was unable to control or prevent the contractions produced by prostigmin.

Method B.

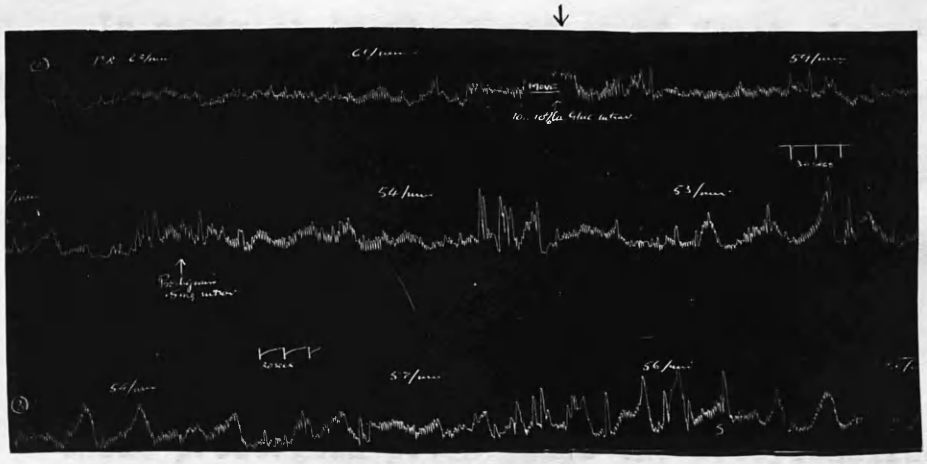


Figure 80.

Calcium gluconate 10 c.c. given at arrow in Tracing 1, prostigmin 0.5 mg. at arrow in Tracing 2.

The tracing (Figure 80) shows the results obtained. The calcium was given first and fifteen minutes later 0.5 mg. prostigmin intravenously. Prior to the calcium administration tonus changes were occurring and on these the drug exercised its usual sedative action. The prostigmin given subsequently produced a motor effect as was expected. The calcium slowed the pulse by two beats per minute, the prostigmin produced a further fall of five beats per minute.

The above experiment again shows that two drugs may have the same action on one organ, in this case the

heart, and a different action on another, the stomach, the calcium having a sedative, the prostigmin an excitor effect.

In contrast to the findings of Veach, Lauer and James, the results obtained from the present investigation may be summed up as follows.

(1) Prostigmin in a dose of 0.5 mg. intravenously has in every case an excitor action on the gastric movements with a slowing effect on the pulse-rate.

(2) A large dose of atropine can prevent the action of prostigmin. This is due to the fact that while prostigmin potentiates the acetylcholine effect on the parasympathetic nerve-endings, atropine prevents the acetylcholine action.

(3) The action of atropine on the gastric motility is not altered by previous prostigmin injection.

Further investigations consisted in the giving of calcium and atropine after prostigmin. The experiment consisted in giving a patient with a normal stomach 0.5 mg. prostigmin; this was followed thirty-five minutes later by 0.6 mg. (1/100 gr.) atropine sulphate intravenously and twenty-five minutes after this 10 c.c. 10% calcium gluconate was given by the same route. The prostigmin produced a motor effect on the gastric motility in ten minutes, slowing the pulse-rate by two beats per minute in ten minutes, the atropine given during relative quiescence caused no change in that condition, quickening the heart by four beats per minute in five minutes. Similarly,

calcium administration was accompanied by no alteration in gastric motility, but caused slowing of the pulse-rate of four beats per minute in ten minutes. No unusual effect was found; the drugs all produced their expected action.

It has been shown previously that small doses of atropine produce a different effect from large doses. It was decided then to give a small dose of atropine before prostigmin and after prostigmin, in order to see if any change in action of either drug was produced.

Two experiments were performed. In the first, 0.5 mg. prostigmin was given intravenously and ten minutes later 0.1 mg. atropine by the same route. The prostigmin produced no apparent effect as the atropine was given within a reasonable latent period. When the atropine was given, a motor effect was produced which appeared to be due to the combined action of the prostigmin and atropine.

In a second investigation, 0.1 mg. atropine was given intravenously followed in fourteen minutes by 0.5 mg. prostigmin given in a similar fashion. The atropine injection was followed by a stimulant action on gastric motility. This effect was greatly increased by the prostigmin. In both cases, the atropine and prostigmin

injections were followed by a slowing of from six to eight beats per minute.

These actions were in accordance with the previous statements, atropine in small doses having a motor action on the stomach and slowing the pulse, prostigmin having the same effect but acting more slowly and more powerfully. No reversal phenomena were seen. This experiment may be taken to support the view that small doses of atropine stimulate the parasympathetic nerves, and the greatly increased motor effect seen in the second result was due to additional stimulation by prostigmin.

The following experiment was accordingly tried.

A normal healthy patient was given 1/10 mg. of atropine; thirty-five minutes later 0.5 mg. prostigmin; and twenty-five minutes later 0.4 mg. (1/50 gr.) of atropine, all by the intravenous route.

The first atropine injection produced a slight motor effect accompanied by a fall in pulse-rate. The prostigmin injection markedly increased the stimulant action, and the last injection of atropine caused an immediate cessation of gastric contractions.

As is seen in the tracing (Figure 81), all these drugs behaved as would be expected from the previous results obtained.

Method A.

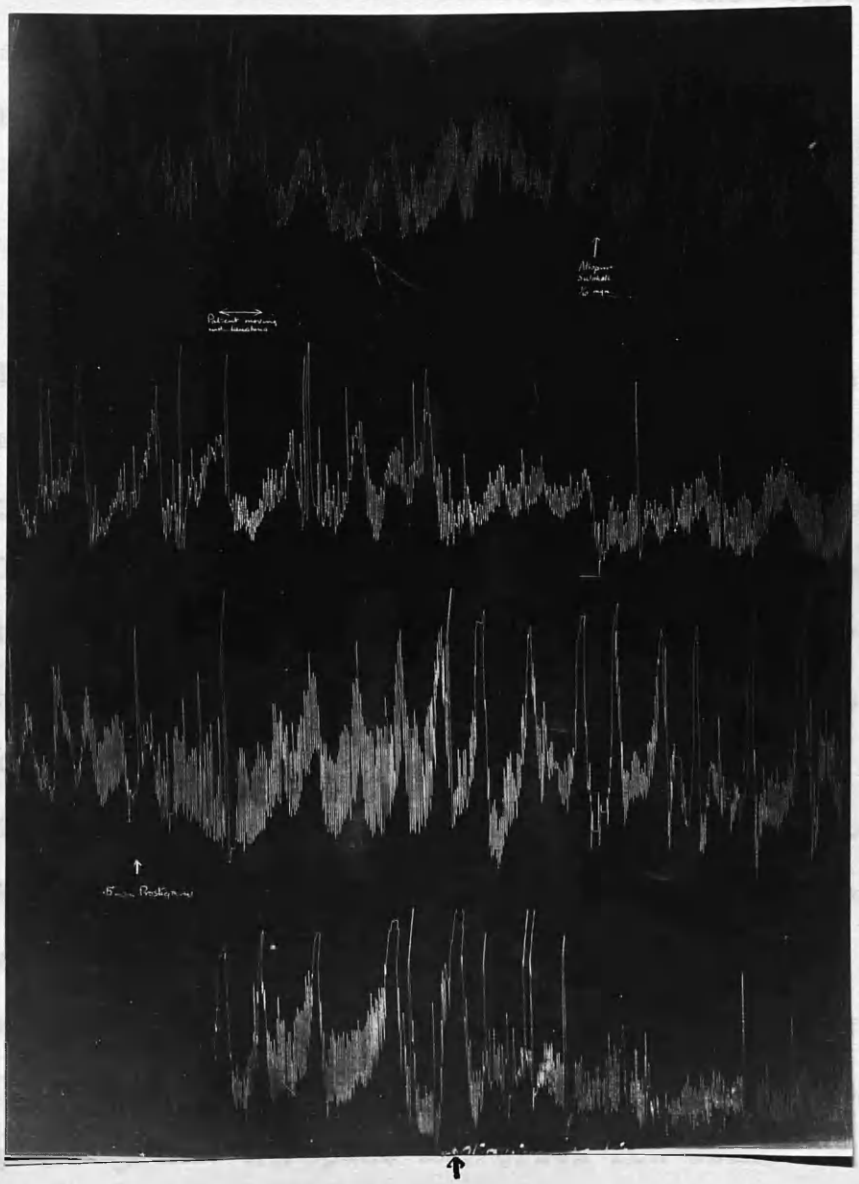


Figure 81.

Atropine Sulphate 1/10 mg. in Tracing 1, prostigmin 0.5 mg. in Tracing 3, and atropine sulphate gr. 1/150 in Tracing 4.

It is evident, therefore, that small doses of atropine do not change the action of prostigmin and conversely the atropine effect is not altered by previous prostigmin administration. The findings also show that small doses of atropine stimulate the parasympathetic nerve endings, while larger doses paralyse them.

SUMMARY

The results of other writers have been examined and experimental evidence has been adduced in order to explain why their conclusions are at variance with my own. No reversal of action of any of the drugs has been found. All the substances have behaved as would be expected from the previous experiments. Prostigmin has been shown to have an excitatory effect on gastric movements and to cause slowing of the pulse. This has been attributed to a potentiation of the liberated acetylcholine on the parasympathetic nerve endings. It has been confirmed that atropine has a double action depending on the dosage used. No reversal of its action has been produced by premedication with prostigmin. Atropine exercises its usual effect provided a reasonable amount of time separates the two injections. The reason for this is that prostigmin sometimes takes twelve minutes to exert its action when given intravenously.

SECTION 6.

THE ACTION OF ADRENALINE.

The action and uses of adrenaline are well known: it appears to stimulate the nerve endings of the sympathetic nerves. Bennett(1923) declared that adrenaline, given either hypodermically or added directly to the stomach, produced negative effects on gastric secretion and motility. Tenzner and Turolt(1921) stated that adrenaline had an inhibitory effect on surviving human stomachs in physiological saline. Danielopolu(1930) found that adrenaline by intravenous administration in very small doses stimulated the parasympathetic nerve supply increasing gastric contractions. Larger doses had apparently little, if any, effect. By increasing the dose further, he found that the adrenaline stimulated the sympathetic nerves and decreased gastric activity. Dickson and Wilson(1925) supported the view of Carlson(1916) that adrenaline inhibited gastric contractions.

It has been noted previously that the action of atropine depends on the dose. In view of this, varying amounts of adrenaline were employed here. The first range of dosage was from 1 c.c. of 1/400,000 solution to 1 c.c.

of 1/40,000 by intravenous injection.

The second method of investigation was by the subcutaneous injection of 10-15 minims of the Liquor Adenalinae Hydrochloridi (B.P.)

Six subjects in good health and with no evidence of gastric disease were each given 1 c.c. of 1/400,000 solution of adrenaline intravenously. In two subjects, the adrenaline produced what appeared to be a slight stimulant action, the frequency and amplitude of the contractions being increased. (Figure 82). No change in the heart-rate was noted in these cases. In four subjects, no effect on the fasting contractions was seen; but in two of these the pulse-rate was reduced by three and four beats per minute respectively at the end of five minutes; the other two subjects showed no change in the pulse.

Method B.

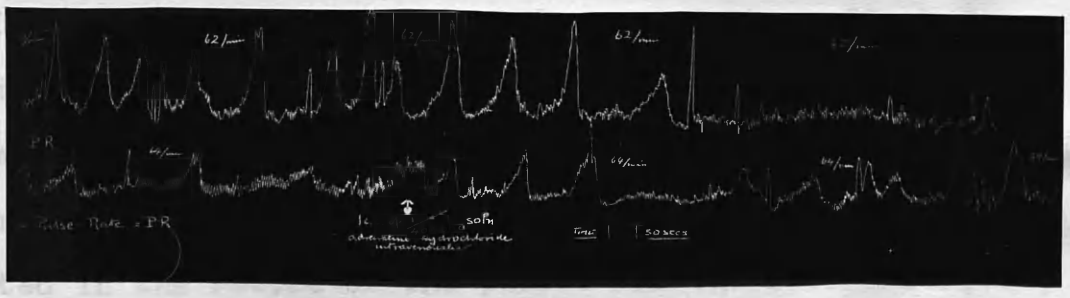


Figure 82.
At arrow in Tracing 1, 1 c.c. of 1/400,000 adrenaline hydrochloride solution given intravenously.

In the next experiment, 1 c.c. of 1/200,000 solution of adrenaline was given intravenously to one healthy subject, and it produced a sedative effect on the fasting contractions. (Figure 83). The contractions diminished in frequency from two in four minutes before the adrenaline, to two in six minutes, after the injections. No change was noted in the pulse-rate.

Method B.

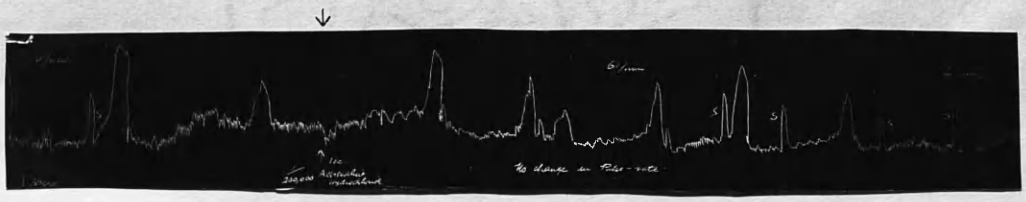


Figure 83.

At arrow, 1 c.c. of 1/200,000 adrenaline hydrochloride solution given intravenously.

In two subjects who were given 1 c.c. of 1/100,000 solution intravenously, a sedative effect was produced on the gastric movements. In the first case, complete cessation of contractions occurred in eight minutes. (Figure 84). On this occasion, no change was noted in the record of the pulse. In the second subject, the contractions continued but were of a lower amplitude.

The pulse-rate was slowed three beats per minute in five minutes, but this lasted only fifteen minutes.

Method B.

2.

1.

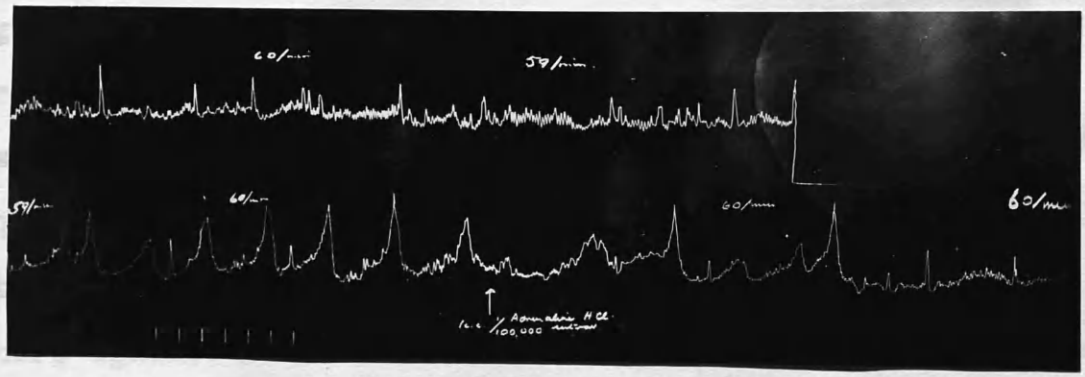


Figure 84.
At arrow in Tracing 1, 1 c.c. of 1/100,000 adrenaline hydrochloride solution given intravenously.

In the four subjects who received 1 c.c. of 1/40,000 solution of adrenaline intravenously, all showed a sedative effect on the gastric motility; this was sometimes merely a reduction in the frequency and amplitude of contractions but in others there was complete cessation of movement. Cessation occurred in two cases, and lasted for twenty minutes. The pulse-rate was unchanged in two of the subjects, and in two others, it showed a slight

quickening of from three to four beats per minute, five minutes after injection.

When the results are reviewed, it is clear that there is no support for the view that a change of action occurs with varying dosage. It is true that with small doses of from 1 c.c. of 1/400,000 to 1 c.c. of 1/100,000, two out of nine cases showed a slight stimulant effect on gastric motility. This, however, was probably a chance result due to the administration of adrenaline coinciding with a period when the contractions began to be more frequent and of higher amplitude. As regards pulse-rate, in three of the nine cases a slight decrease was noted, but here again, it would be unwise to lay much stress on this finding.

There appears then to be no proof that the first action of adrenaline is that of a parasympathetic stimulant. The small doses of adrenaline appear, except in rare cases, to produce no effect until the solution is sufficiently concentrated to cause a sympathicomimetic action.

In dosage of ten to fifteen minims by subcutaneous injection, adrenaline appears to have a constant effect. Three subjects were given ten minims, and one fifteen minims, and the results were as follows:-

Case I.
Two minutes after the injection, there was temporary inhibition of gastric movements lasting fifteen minutes. The pulse-rate increased by four beats per minute in five minutes following the adrenaline.

Case II.
Six minutes following the injection, cessation of contractions occurred and lasted 1 hour. The pulse-rate rose by three beats per minute ten minutes after the injection.

Case III.
In ten minutes there was a temporary inhibition of gastric contractions, which lasted for fifteen minutes. The pulse-rate was unaltered.

Case IV.
Fifteen minims were given, and in eight minutes cessation of movements occurred and lasted for one hour; the experiment was then stopped. (Figure 85). The pulse-rate rose three beats per minute in fifteen minutes.

Method A.

1.

2.

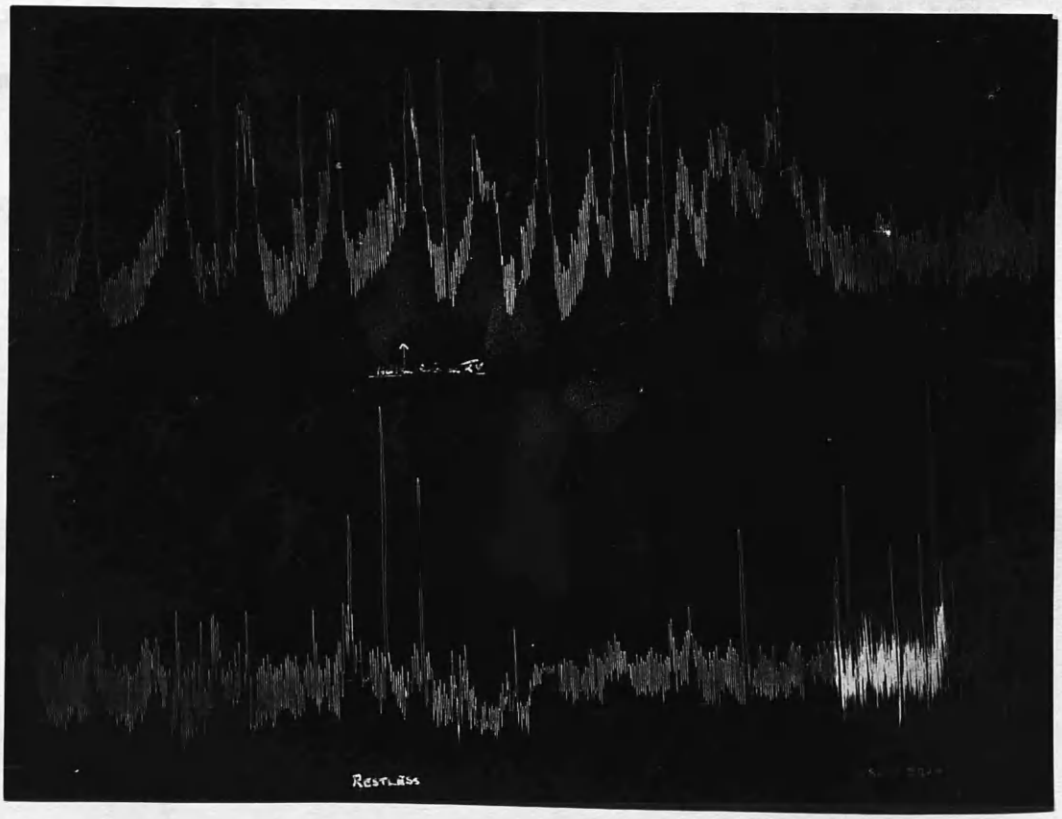


Figure 85.

At arrow in Tracing 1, fifteen minims of liquor adrenalinae hydrochloridi given by subcutaneous injection.

The conclusion is that adrenaline by subcutaneous injection produces constant effects, (1) a quietening

of gastric movements, and (2) a slight quickening of the pulse.

It appears to be in agreement with the findings to state that adrenaline acts by stimulating the sympathetic nerve endings. Thus the giving of adrenaline and the stimulation of the sympathetic nerves produces the same result on the gastric fasting contractions. The effect on the stomach occurred with doses which do not produce marked quickening of the heart.

SECTION 7.

(a) ACTION OF STRYCHNINE ON GASTRIC MOTILITY

Bennett,(1923) quoting Berti at considerable length, gives the following results for varying doses of strychnine nitrate administered by mouth. The method used was by x-ray screening with a contrast medium. One half milligram of strychnine caused increased peristalsis, which continued for one hour with more rapid emptying of the stomach. One milligram produced a marked increase in the gastric movements. After one hour the contraction of the pyloric part was sufficient to delay emptying; the peristaltic waves were then feeble. Two to six milligrams gave gradually more violent contractions with spasm of the pylorus, till eventually the general hypertonus was so great that peristaltic movements were prevented. Hypodermic administration resulted in the same effects being produced with smaller dosage.

Bennett(1923) himself stated that small doses of strychnine had a beneficial effect on gastric atony. Dickson and Wilson,(1925) using a balloon method, maintained that strychnine causes increased movements of the

stomach. Varga(1936) refers to the "normalising" action of strychnine on the stomach in children: no matter whether the stomach emptied too quickly or too slowly, the emptying time became normal after treatment with strychnine.

Clark(1940) states that strychnine has no effect on movements of the stomach even when given in tetanic doses. Bastedo(1932) gives as his opinion that in full therapeutic doses, strychnine tends to increase the tone of the stomach and intestines, the height of the hunger contractions and the peristaltic response to food.

In the present investigation, ten cases were studied; each patient was given strychnine hydrochloride, gr. 1/20 subcutaneously. As usual, the patients were fasting, no food being given for at least five hours previously. Strychnine, in this dosage, appeared to have the power of initiating contractions in stomachs, showing a phase of relative quiescence. In eight cases, these contractions appeared from five to fifteen minutes after injection, and lasted from twenty to forty-five minutes. The movements so produced were strong and the interval between each wave tended to become shorter towards the end of a period of contractions. (Figure 86).

Method A.

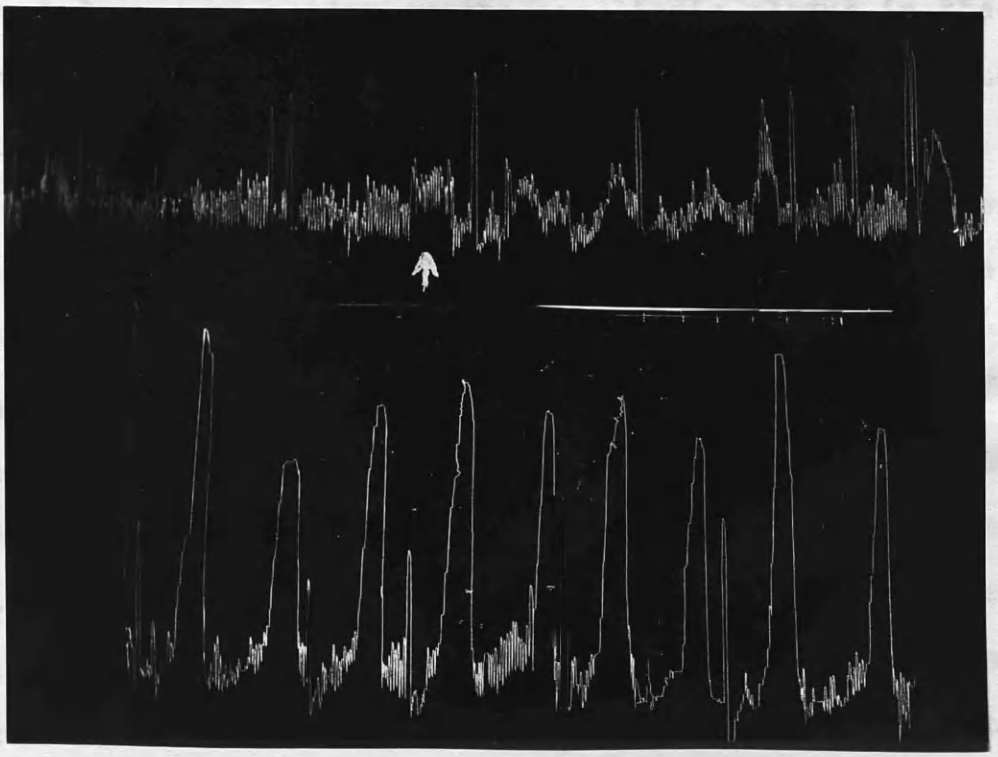


Figure 86.

At arrow in Tracing 1, strychnine gr. 1/20 given subcutaneously.

In two subjects, an injection of strychnine was given after a period of contractions had lasted thirty-five and forty-five minutes respectively, but in spite of the strychnine injection a period of

quiescence occurred. This was thought to be due to fatigue of the stomach muscle. In this dosage strychnine had no effect on the pulse-rate.

Cushny(1936) states that after absorption, strychnine is said to increase the movements of the bowel from some action on the ganglionic plexus in the bowel wall. To explain the action, Bastedo(1932) quotes Ginsburgh and Tumpowsky, who found an increase in the tonus of the stomach and increased height of the hunger contractions in a dog after a sufficient dose to cause excitability and increased tonus of the abdominal muscles. They found that the stomach showed the same effect after the severance of all connections with the central nervous system, and stated that the action then is on Auerbach's plexus. Langley and Magnus(1905) found that a weak solution applied to the ganglia of Auerbach's plexus caused stimulation. The evidence appears to indicate that strychnine has a stimulant action on the fasting stomach and that this is due to stimulation of Auerbach's plexus.

(b) THE "TONIC" ACTION OF STRYCHNINE

Strychnine has frequently been described as the only true tonic. In this investigation, it was decided

to try and obtain information with regard to the effect of strychnine after absorption. It has been demonstrated that a large single dose of strychnine increased the activity of the fasting contractions. It is noteworthy, however, that no complaint of hunger was associated even with these increased movements. The drug was injected parenterally in order to avoid the "bitter" action which accompanies oral administration. Sollmann(1936) stated that strychnine by hypodermic injection is two to eight times more active than by oral administration.

Four main lines of investigation were used:-

(1) Ten patients were given strychnine by subcutaneous injection, until amounts varying from 22-100 mg. had been given. Before the strychnine was given the weight of the patient was taken. A haemoglobin estimation (Sahli) with red and white cell counts were performed. The serum protein and a differential white cell count of 500 cells done on an empty stomach were noted. The same investigations were performed after the course of strychnine. When the weights are taken into consideration, it must be noted that all these patients were on full ward diet and were all able to obtain more food on request. In addition their weight had reached a stationary level before the experiment was started. In analysing

Table XVIII. shown on the following page, it was seen that any changes that were found were within the limits of spontaneous physiological diurnal variation. The haemoglobin percentage fell from two to ten points in seven cases, gained five to eight points in three cases and remained stationary in one case. The red cell count varied slightly falling in seven cases, and gaining in four cases. The white cells were fewer in number in six cases, more numerous in four and remained the same in one case. An analysis of the differential count revealed an increase in the polymorphonuclear leucocytes in four cases, a decrease in five cases and no change in one case. Similar results showing no constant change were found in comparing proportions of the other types of cells. The level of the serum protein dropped slightly in six cases, gained a little in four and remained stationary in one. Very little change was noted in the weights of the patients although some of them were below weight before the strychnine was given. Five cases showed an increase in weight of one to five lbs., three cases dropped one lb. and in two cases the weight remained stationary. From these results it appeared that strychnine excited very little change in the blood or the weight of the patient.

T A B L E XVIII.

Name	Date	HB% Sah-li	R.B.C. X 10^6	W.B.C.	Differential Count						Serum Pro-tein	Weight	Total mg. of Strychnine
					Polys.	S. Lymph	L. Lymph	Eos.	Bas.	Mon.			
Mrs.W.(Pre-strychnine	20.12.38	75	3.8	7,600	69	13	7	3	.5	7.5	6.55%	6 st.13 lbs.	22 milli-
(Post-strychnine	24.12.38	75	3.7	7,400	66	14	5	3	1	11	7.63	7 st. 1 lb.	grams.
Mrs.G.(Pre-strychnine	17.1.39	65	3.6	9,200	66	16	11	2	1	7	8.28	7 st. 6 lbs.	50 mill-
(Post-strychnine	27.1.39	62	3.5	6,000	68	13	8	2	.3	8	7.42	7 st. 9 lbs.	grams.
Mrs.D.(Pre-strychnine	15.1.39	80	4.0	8,000	63	23	3	4	1	6	8.28	7 st.13 lbs.	100 milli-
(Post-strychnine	14.2.39	70	3.9	7,200	58	30	4	3	.5	3.5	7.47	7 st.13 lbs.	grams.
Mr.McD.(Pre-strychnine	19.1.39	90	4.3	4,000	53	26	10	.3	.3	10	9.14	12 st.10 lbs.	28 milli-
(Post-strychnine	26.1.39	85	4.1	4,000	57	18	7	2	-	12	8.06	12 st. 9 lbs.	grams.
Mr.M.(Pre-strychnine	4.2.39	70	3.8	4,000	66	10	7	3	.3	11	7.85	9 st.12 lbs.	72 milli-
(Post-strychnine	25.2.39	75	4.3	9,600	66	17	5	1	.5	10	7.85	10 st. 2 lbs.	grams.
Mrs.S.(Pre-strychnine	26.1.39	60	3.6	4,600	62	14	8	3	1	12	7.42	10 st. 7 lbs.	100 milli-
(Post-strychnine	13.2.39	68	4.0	5,200	61	12	10	3	1	12	7.85	10 st. 7 lbs.	grams.
Mrs.F.(Pre-strychnine	30.1.39	80	4.6	7,600	70	12	7	.1	-	7	7.42	6 st. 4 lbs.	90 milli-
(Post-strychnine	14.2.39	78	4.4	4,800	66	19.5	6	.5	1%	7	6.98	6 st. 3 lbs.	grams.
Mrs.H.(Pre-strychnine	21.2.39	93	4.7	7,600	71	11	8	2	.5	7	8.06	11 st. 6 lbs.	100 milli-
(Post-strychnine	21.3.39	90	4.9	6,200	72	10	9	2	.5	6	8.49	11 st. 7 lbs.	grams.
Mrs.B.(Pre-strychnine	1.3.39	80	4.0	8,800	68	12	10	1	1	8	8.06	8 st. 2 lbs.	78 milli-
(Post-strychnine	15.3.39	73	4.8	6,600	67	14	11	2	.5	6	7.20	8 st. 1 lb.	grams.
Mrs.G.(Pre-strychnine	30.5.39	89	4.1	4,000	58	28	6	1.5	.5	6	8.28	10 st. 4 lbs.	100 milli-
(Post-strychnine	19.6.39	83	4.2	5,200	59	25	7	1.5	.5	7	8.06	10 st. 7 lbs.	grams.
Mrs.D.(Pre-strychnine	5.12.38	77	4.7	6,000	-	-	-	-	-	-	7.85	-	70 milli-
(Post-strychnine	20.12.38	85	4.5	7,600	-	-	-	-	-	-	8.49	-	grams.

(2) Nine patients were followed with progress notes and frequent blood pressure readings, a control period being taken before the strychnine was started. The pulse-rate was noted in detail in three cases. Test-meals and blood sugar curves were performed before and after strychnine treatment.

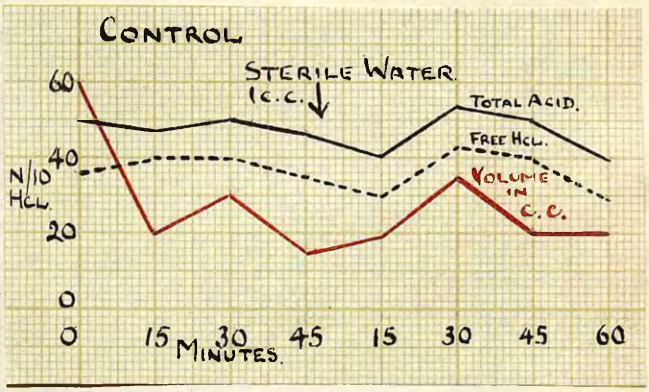
From the clinical notes, pulse-rate and blood pressure readings, no change was found to occur during or following the strychnine therapy. The case reports and results are shown in the appendix. No alteration was noted in the blood sugar curves. In seven test meals performed before and after strychnine, the emptying time was shortened in four cases and unaltered in three. In one case a diminished amount of free hydrochloric acid was found after the strychnine. In another, achlorhydria shown before the strychnine treatment was replaced by a small amount of free hydrochloric acid. The other charts showed no significant change in acidity.

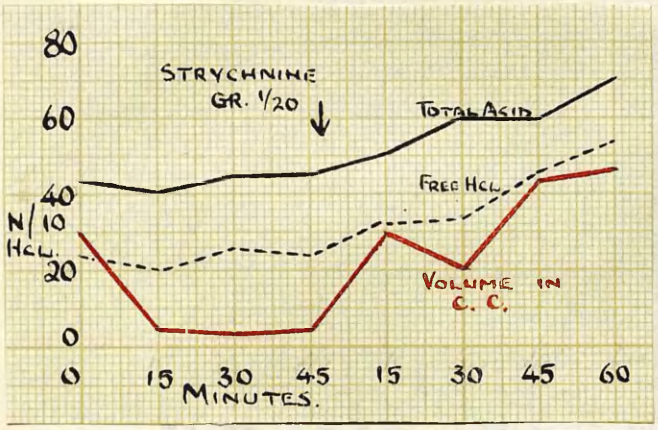
(3) The effect of a single dose of strychnine by subcutaneous injection on the fasting juice was next studied. Four specimens of fasting juice were taken at fifteen minute intervals, then strychnine gr. 1/20 was given and the procedure repeated. In three cases of achlorhydria, the strychnine produced no secretion of

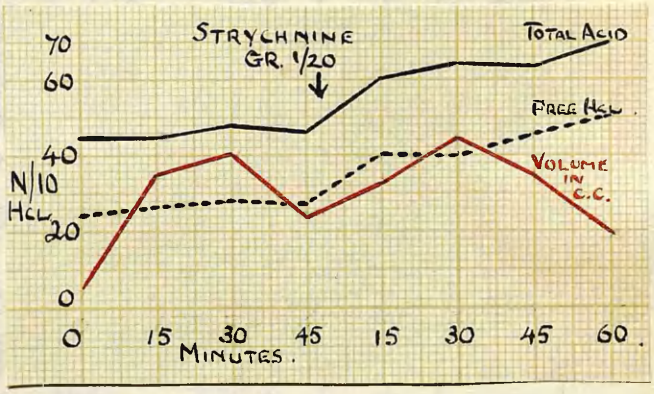
hydrochloric acid. In four cases of normal acidity, the strychnine produced an increase in both volume and acidity, shown in the graphs. (Figure 87). The average volumes per specimen of the four cases before strychnine were 12, 17, 28 and 27 c.c. and after strychnine 35, 38, 44 and 34 c.c. respectively. The highest levels of free hydrochloric acid before strychnine expressed in c.c. of N/10 hydrochloric acid were 26, 25, 29 and 62, after strychnine these figures were 52, 57, 50 and 68 respectively.

(4) The effect of a single injection of strychnine gr. 1/20 on the white corpuscles was next studied. Sollmann(1936) states that in vitro phagocytosis is hindered by strychnine, but agrees that the doses used were much in excess of those possible in vivo. Edmunds and Lloyd(1923) found an increase in the white cells in intact normal dogs, which they suggested was due to a discharge of adrenaline caused by the strychnine.

The method employed here was to give 1 c.c. of sterile water subcutaneously to a subject whose white cell and differential count had been performed that morning, and who was fasting. White blood cell counts and differentials were performed at half-hourly intervals for three hours and the next morning instead of sterile water,


CONTROL
STERILE WATER
1 C.C.
TOTAL ACID.
FREE HCL.
VOLUME IN C.C.
N/10 HCL.
60
40
20
0
0 15 30 45 15 30 45 60
MINUTES.


STRYCHNINE GR. 1/20
TOTAL ACID
FREE HCL.
VOLUME IN C. C.
N/10 HCL.
80
60
40
20
0
0 15 30 45 15 30 45 60
MINUTES.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TOTAL ACID
FREE HCL.
VOLUME IN C.C.
N/10 HCL.
70
60
40
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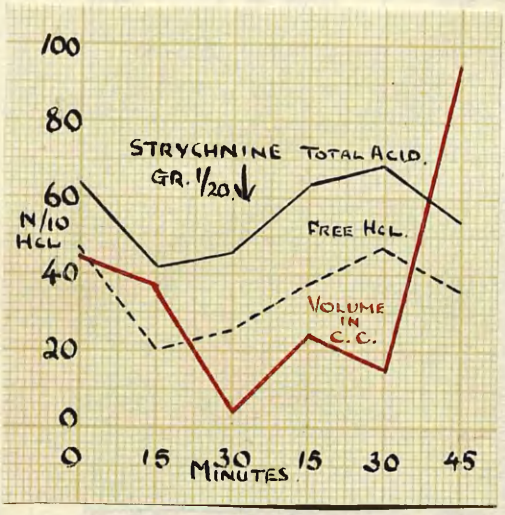
0 15 30 45 15 30 45 60
MINUTES.


STRYCHNINE GR. 1/20
TOTAL ACID.
FREE HCL.
VOLUME IN C.C.
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100
80
60
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MINUTES.

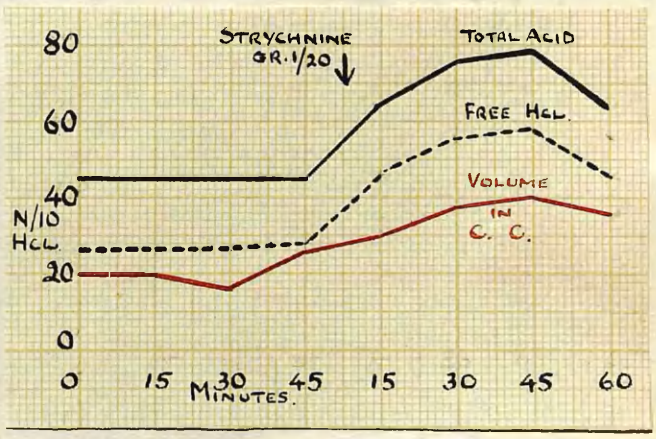

STRYCHNINE GR. 1/20
TOTAL ACID
FREE HCL.
VOLUME IN C. C.
N/10 HCL.
80
60
40
20
0
0 15 30 45 15 30 45 60
MINUTES.

Figure 87.

strychnine gr. 1/20 was given and the same procedure carried out. As will be seen from Table XIX., in two cases no significant change in the white corpuscles was noted.

T A B L E XIX.

STRYCHNINE ON WHITE BLOOD CELLS

Case I.

Control.

Time	W.B.C.	Differential					
		Polys.	Small Lymphs	Large Lymphs	Eosin.	Mono.	Baso.
9.30.	6,200	63	26	2.6	1.4	7	-
9.35.		Injection of 1 c.c. sterile water.					
10.	6,400	64	24	4	1	7	-
10.30	6,400	66	23	2.2	1.3	7.2	.3
11.	6,200	60	24	5.2	1.4	8.4	1
11.30	6,200	63.5	22.5	5.3	1.2	6.5	1
12.	6,200						
12.30	6,000	59	25	6	.5	9	.5
Strychnine given							
9.30.	6,800	62	25	4	1	8	-
9.35.		Strychnine gr. 1/20 hypodermically.					
10.	7,000	56	27	6	2	9	-
10.30.	6,800	53	26	10	1.3	9	.7
11.	6,600	61.2	21.9	5.8	.5	9.6	1
11.30.	6,000	59.5	24.5	6.8	.5	8.6	.4
12.30.	8,000	70.	13.6	2	.8	12	1.6

Case II.

Control.

9.30	6,000	59	15	15	2	7.7	1.3
9.35		1 c.c. sterile water by injection.					
10.	5,900	70	12	8	2.7	7	.3
10.30.	6,000	69	8	14	1.5	6.5	1
11.	5,600	70	7.5	12	2	7.5	1
11.30.	6,000						
12.	5,900	69	10.5	9.5	2	7.5	1.5
12.30.	6,100	59	15.	17.	1.6	6.5	.9
Strychnine given							
9.30.	6,400	58	18	12	2	9	1
9.35.		Strychnine gr. 1/20 given hypodermically.					
10.	6,200	59	12	15	2	11	1
10.30	5,200	60	13	13	4	7	3
11.	5,200	58	13	16	4	8.7	.3
12.	5,400	57	13	20	3	6	1
12.30.	5,600	66	13	12	2.5	6	.5

SUMMARY

From these investigations on strychnine, only three facts emerge, the first is that it has been shown by the balloon method that strychnine appears to initiate gastric movements, the second that this drug appears to hasten the emptying time of the stomach contents in some cases, and the third that it appears to stimulate the fasting gastric juice. In cases of achlorhydria, the strychnine did not cause the production of free hydrochloric acid.

No evidence has been produced to justify the parenteral administration of strychnine as a tonic; no alteration in the haemoglobin level and no marked change in the weight occurred after strychnine therapy. The minor actions noted cannot be assumed to play any important part in improving the general condition of the patient.

S E C T I O N 8.

THE ACTION OF MORPHINE

Myers,(1939) after giving a survey of the literature with regard to the effect of morphine on the stomach, described the results of his experiments by stating that morphine has a variable effect on the gastric motility. This author used the balloon method with an apparatus of his own on decerebrate cats. Meyer and Gottlieb(1926) quoted Hirsch, who found in dogs with a duodenal fistula, that the emptying time of the stomach was greatly delayed by morphine. Magnus,(1908) working with cats and dogs and using an x-ray method, stated that a few centigrams of morphine caused a marked delay in the flow of contents from the stomach. This, he explained, was due to a dilated fundus with a strongly contracted pyloric antrum. He found that small doses (5 mg. subcutaneously) usually caused an increase of gastric peristalsis, without spasm of the sphincter and that a more rapid emptying of the stomach than usual occurred.

Bisgard and Johnson(1939) showed in man that morphine sulphate gave a marked increase in tonus in both stomach and small bowel. In the stomach an increase

in the frequency and amplitude of contractions occurred.

In the present investigation morphine sulphate gr. 1/6 was given intravenously to three subjects.

In the first case immediately after the injection, a phase of relative quiescence occurred lasting seven minutes and followed by a period of increase in the frequency and amplitude of contraction of twenty minutes' duration. This was in turn followed by a rest pause. (Figure 88).

In the second case immediately after the drug was given, a rest period lasting ten minutes occurred. This was followed by another ten-minute phase of increased frequency and amplitude of contractions. A period of relative quiescence followed this. (Figure 89).

Method B.

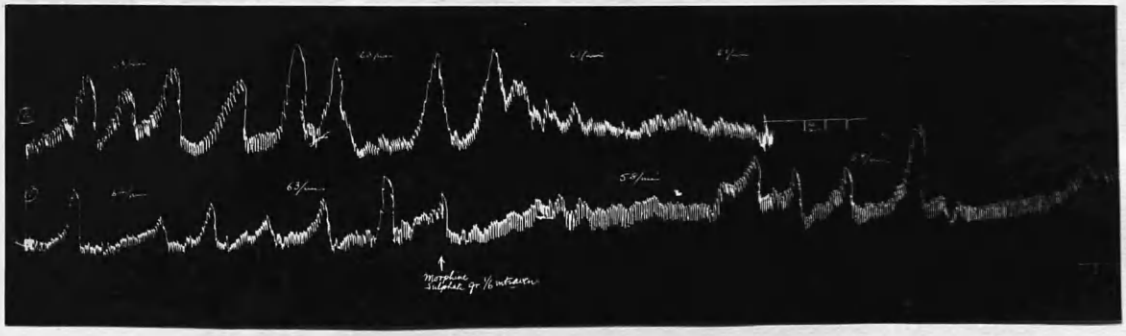


Figure 88.
At arrow in Tracing 1, Morphine Sulphate gr. 1/6 given intravenously.

Method B.

3.

2.

1.

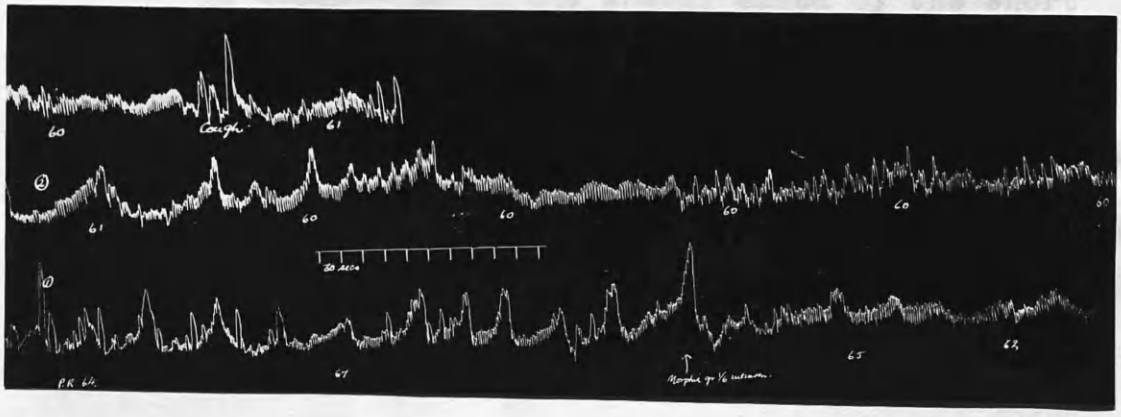


Figure 89.
At arrow in Tracing 1, Morphine Sulphate, gr. 1/6 given intravenously.

In the last case an immediate rest period of six minutes' duration was noted after the morphine administration. This was followed by increased contractions lasting twenty-two minutes. This phase was succeeded by a period of rest.

In cases 1 and 3, the pulse was slowed by three and five beats per minute respectively after the injection, and no alteration was noted in case 2.

In all the experiments here, the first result of the morphine has been to produce a rest period of from

six to ten minutes, and this in turn has been followed by a phase of increased frequency and greater amplitude of contractions of from ten to twenty-two minutes. The final result in all cases was quiescence.

It appears as if the energy saved by the short period of preliminary rest is liberated to cause greater movements which, tiring the stomach, finally result in quiescence. It seems that in this dosage morphine combines the two different effects noted by Magnus. The mode of action of morphine is unknown.

It would be erroneous to conclude from these experiments that morphine is contra-indicated as a sedative in cases of haematemesis. These subjects used here had empty stomachs which were normal. The patient suffering from haematemesis has blood and blood clot in his stomach and, in addition, some pathological condition is usually present. No information regarding the response produced by morphine on this type of case has been produced. It can be seen, however, that a very slight exaggeration of the gastric activity found in the normal person would result in the vomiting and gastric upset seen in some cases of morphine idiosyncrasy.

SECTION 9.

(a) THE ACTION OF HISTAMINE

This substance has been chemically demonstrated in extracts of the mucous membrance of the small intestine, liver, lung, and posterior lobe of the pituitary body. It has also been found in preparations of ergot.

The main actions are as follows:-

(1) Powerful secretogogue mainly of gastric juice.

(2) Stimulant to smooth muscle, e.g. uterus and bronchioles.

(3) Production of fall in blood pressure due to generalised capillary paralysis.

In anaesthetized dogs, Wolff(1939) found that histamine given intravenously caused a depression of gastro-intestinal tone and motility. In man, Cushny(1936) states that the stomach contracts more powerfully after histamine and that this effect is not counteracted by atropine. Ivy and Vloedman,(1923) using dogs, found by Carlson's balloon method that histamine produced no effect on the gastric motility in dosage of 0.5 - 1 mg. Dickson and Wilson(1928) reported that histamine, given as 2 c.c. of 1/1000 solution (2 mg.) subcutaneously, caused an increased peristalsis and rate of emptying. These observations were made by means of repeated barium meals; the

intragastric balloon was used only occasionally to determine changes in pressure. Neidhart(1935) observed in man that histamine hypodermically in doses of 0.25 - 0.76 mg. limited gastric movement.

With the usual experimental precautions, tracings taken with the intragastric balloon show after the subcutaneous injection of 1 mg. histamine an immediate and complete cessation of gastric contractions. This result was obtained in five cases. The period of rest produced lasted usually at least forty-five minutes and was accompanied by a quickening of the pulse. This increase in pulse-rate ranged from nine to eighteen beats per minute faster in the first ten minutes after the injection and the quickening lasted for thirty-five to fifty minutes. The tracings show the results obtained. (Figures 90, 91). There were no unpleasant symptoms such as headache or nausea following the injection of the histamine.

Method A.

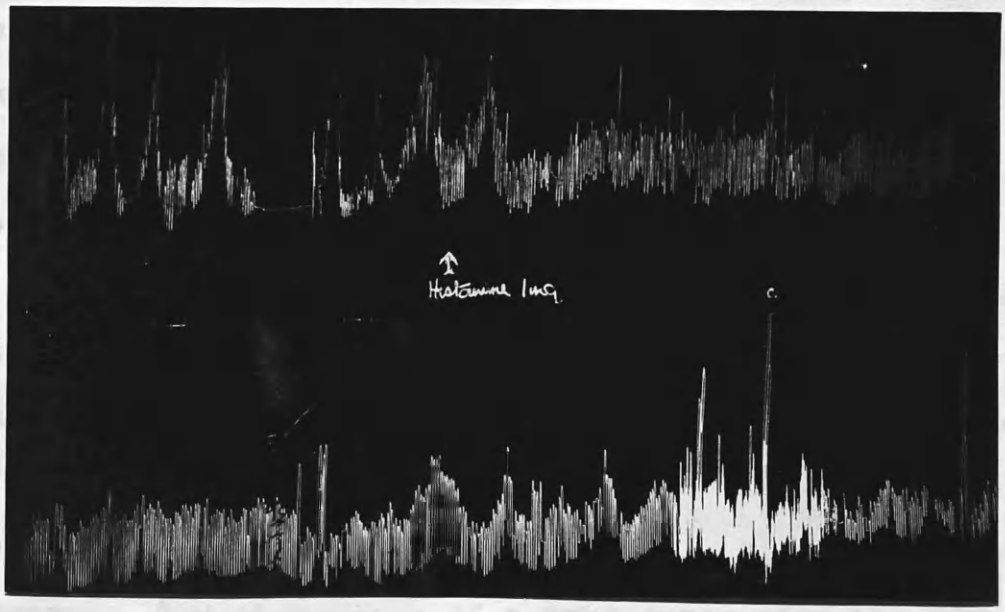


Figure 90.

At arrow in Tracing 1, 1 milligram of histamine given subcutaneously.

Method A.

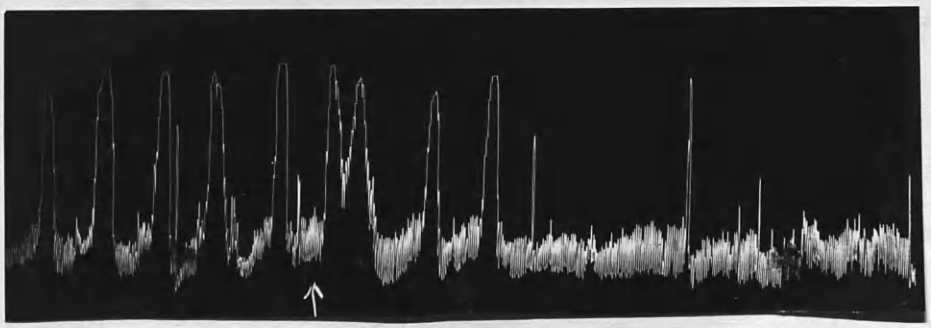


Figure 91.

At arrow, histamine 1 mg. given subcutaneously.

The action of histamine on gastric motility may be related to the secretion of gastric juice, which occurs after the injection. It has been shown that water alone if swallowed will inhibit the gastric hunger contractions, and similarly the presence of the gastric juice in abnormal quantity may produce the same effect. This action of histamine is in direct contrast to its usual effect in causing spasm of smooth muscle.

In order to contrast these two effects of the one drug, in two cases four fasting specimens of gastric juice were taken at fifteen minute intervals before and after histamine. Figure 92 shows how striking was the response: both the acidity and volume were markedly increased. The phenomenon of a drug increasing the secretory action of an organ and inhibiting the motility is of considerable interest.

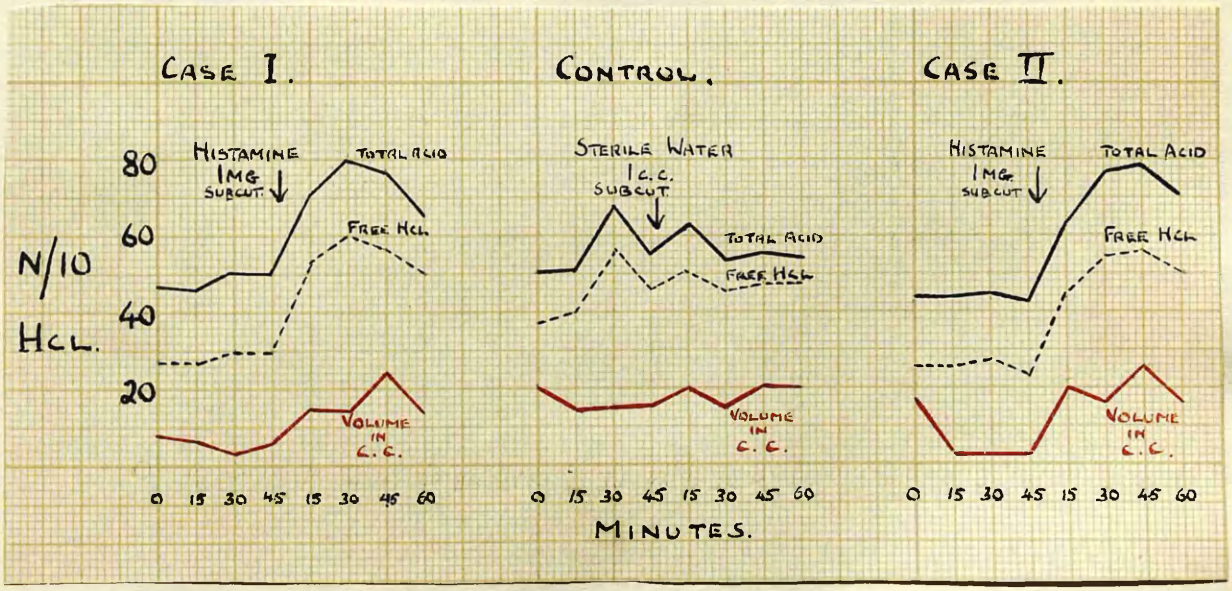


Figure 92.

(b) THE ACTION OF LAROSTIDIN

Histidine hydrochloride, the amino-acid corresponding to histamine has been used in the form of an aqueous solution for the treatment of peptic ulcers. The theoretical basis of the treatment rests on the work of Aron and Weiss.(1933) From experiments on dogs, they suggested that ulcer formation was connected with a deficiency of amino-acids and that this deficiency was corrected by the injection of histidine. Barry and Florey(1936) were unable to substantiate the suggestion of Aron and Weiss. Schürch and Blangey(1936) found that Larostidin, a 40% solution of l-histidine hydrochloride helped to heal gastric ulcers in rabbits. Many clinical reports have been made and as a result the treatment has fallen out of favour. Martin(1936) found in comparing cases treated with histidine with cases treated with the usual diet-alkali, that symptomatic and radiologic response of the patient in the histidine series was not quite as good as that in the diet-alkali series in either the initial or the sustained effect. He concluded that the claims that have been made for this substance are unwarranted. Goodman and Bearg(1938) found from experiments with

segments of the small intestine in organ baths that histidine in physiological concentration has no effect on the tone or motility.

The effect on the gastric motility of intramuscular injections of Larostidin in 5 c.c. doses was tried on three patients with normal stomach. The Larostidin always produced a cessation of contractions in three to fifteen minutes which lasted from thirty to forty minutes. The Larostidin then has the same action as histamine on the stomach but produces no change in the pulse-rate. This sedative action might help to explain why Larostidin relieves the pain of peptic ulceration in some small degree. The tracings show the results obtained. (Figure 93).

Method B.

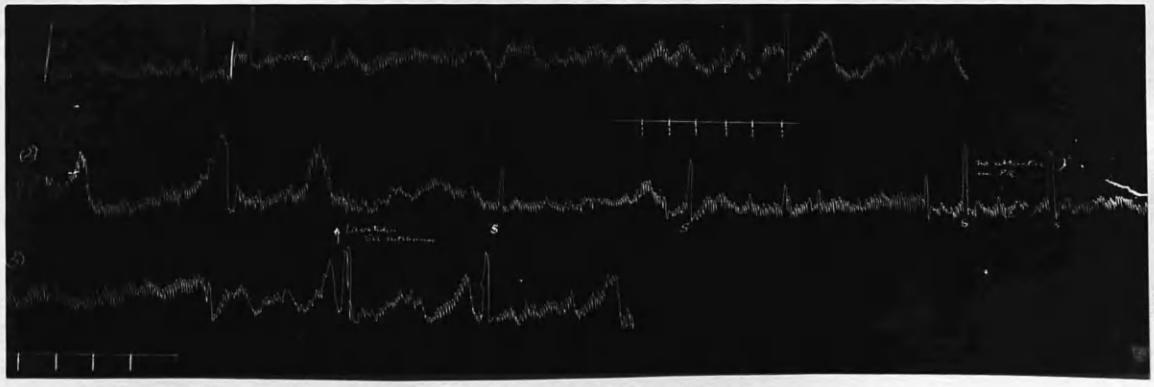
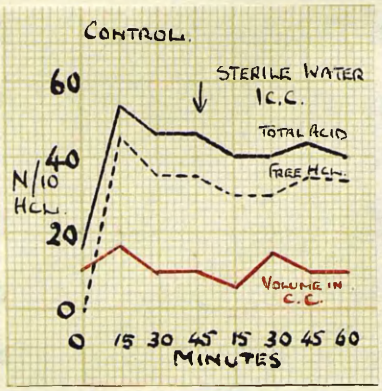
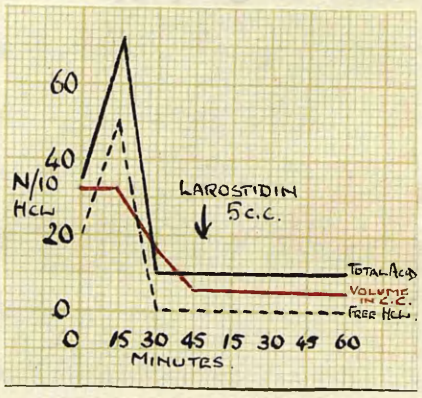


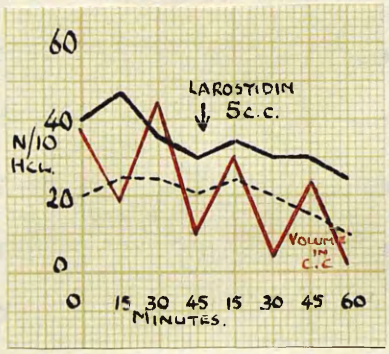
Figure 93.

At arrow in Tracing 2, 5 c.c. of Larostidin given intramuscularly.

In four cases, fasting specimens of gastric juice were taken at fifteen minute intervals for one hour, then 5 c.c. of Larostidin was given intramuscularly and after fifteen minutes, specimens were taken at the same intervals. Figure 94 shows the results obtained. In no instance did this substance appear to cause a production of gastric juice. The average volumes in c.c. before the injection were 20, 20, 29 and 11, and after 9, 3, 15 and 6 respectively. The highest free acidities reached prior to Larostidin administration were 37, 52, and 25, and after 30, 0, and 25 respectively. In one case of achlorhydria no free hydrochloric acid was produced. If Larostidin has any action on the fasting gastric juice it is merely to cause a slight lowering in acidity and a diminution in the amount secreted. Thus Larostidin has the same action as histamine on the stomach movements but a different effect on the gastric juice. This fact seems to strengthen the previous statement that no relation exists between gastric motility and acidity.


CONTROL.
STERILE WATER
1 C.C.
TOTAL ACID
FREE HCL
VOLUME IN C.C.
N/10 HCL.
60
40
20
0
0 15 30 45 15 30 45 60
MINUTES


LAROSTIDIN
5 C.C.
TOTAL ACID
VOLUME IN C.C.
FREE HCL
N/10 HCL
60
40
20
0
0 15 30 45 15 30 45 60
MINUTES


LAROSTIDIN
5 C.C.
VOLUME IN C.C.
N/10 HCL
60
40
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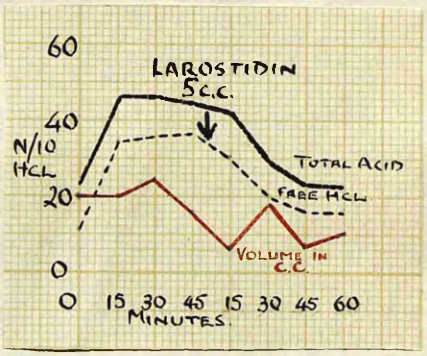
0 15 30 45 15 30 45 60
MINUTES.


LAROSTIDIN
5 C.C.
TOTAL ACID
FREE HCL
VOLUME IN C.C.
N/10 HCL
60
40
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0 15 30 45 15 30 45 60
MINUTES.

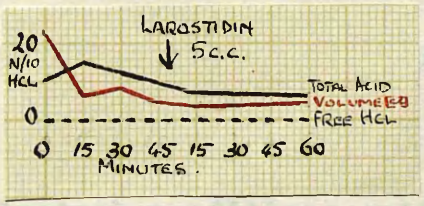
LAROSTIDIN
5 C.C.
TOTAL ACID
VOLUME IN C.C.
FREE HCL
20
N/10 HCL
0
0 15 30 45 15 30 45 60
MINUTES.

Figure 94.

GENERAL SUMMARY

1. By using the human subject an attempt has been made to overcome the possible errors of applying to clinical medicine the results of experimental observations on animals. The method employed that of "Viscerography" is an old one but it has been constantly checked by radiological methods. The balloon used was larger than that described by other authors and the results obtained from the normal fasting stomach agreed, with certain additions, with the previous work done. Certain difficulties encountered are described and the importance of a trained patient free from cough and febrile illness is emphasised. It appears to be true that the fasting stomach is never completely at rest. In the phase which approaches nearest to this, small changes of tone are constantly present. Other types of activity are also described in some detail. The gastric reflexes demonstrated the important part played by the vagus nerve on the extrinsic innervation of the stomach. Mild stimulation of the vagus completely changes the type of contraction.

2. In pathological conditions evidence obtained from a tracing is not sufficient from which to draw a definite conclusion as to the type of lesion. It is felt that too

much stress has been put on this method as a diagnostic aid. Patients with peptic ulcers may have fasting gastric contractions indistinguishable from normal. Certain of these cases had ulcer pain while the recording apparatus was in situ and it was found that gastric contractions alone did not explain the pain in this condition. Other factors suggested were spasm of the pylorus, duodenal contractions, the free acid of the gastric juice, and lastly local oedema, congestion and contraction round the actual ulcer crater.

3. Water which in the normal patient completely stopped the fasting movements was found to cause contractions of the stomach in some cases of peptic ulceration. In others, only a short period of quiescence or a change to tonus waves was found. In no patient with gastric or duodenal ulceration did the normal rest phase occur. This phenomenon is difficult to explain but it suggests increased irritability of the stomach. This finding is considered important because it demonstrates altered sensibility of the raw area to intragastric or intraduodenal stimuli. The water in some cases produced pain, suggesting that the local lesion plays at least some part in the causation of the pain. The part played by sensory

impulses from the lining of the stomach or duodenum is not yet known. The statement that there are no pain fibres in the gastric or duodenal mucous membrane appears to be untrue.

4. No connection between the secretory and motor activity of the fasting stomach has been demonstrated.

5. The action of certain drugs was then studied on the fasting contractions. The most interesting results were found in the case of atropine. Large doses of this drug have the usual and accepted action, i.e. a paralysis of the parasympathetic nerve supply to the stomach and heart. The gastric contractions are arrested and the pulse-rate is quickened. It must be stressed that if the dose given is large enough, all movements of the stomach are completely stopped. It is commonly stated that only abnormal contractions are affected; my own results do not support this. It has been shown that there is an intermediate range of dosage with an inconstant action on the pulse and stomach. In some cases no change occurs, in others there are only slight alterations. Small doses produce a totally opposite action causing a slowing of the pulse and an augmentation and increased frequency of gastric contractions. In addition a peculiar change occurs

when two small doses are given one after the other. The first dose produces its usual effect, i.e. slowing of pulse and increased gastric contractions, whereas the second dose has the effect of a large dose, i.e. quickening of heart-rate and cessation of stomach movements. These phenomena are difficult to explain but it is postulated that atropine in small doses may produce preliminary stimulation instead of paralysis of the parasympathetic nerve-endings. It is possible that with the two small doses, the first stimulates the vagus nerve and also sensitizes it, so that a second similar dose has the effect of a large dose, i.e., it produces paralysis of the parasympathetic system.

The action of other synthetic atropine-like compounds, Trasentin and Syntropan, has been found to be more weakly sedative than atropine on the stomach and without effect on the heart-rate.

5. The action of calcium shows that if the present classification of the autonomic nervous system is accepted it is necessary to postulate that this drug stimulates the parasympathetic nerve fibres to the heart in the same dose in which it excites the sympathetic supply to the stomach. Calcium causes slowing of the pulse and quietening of gastric activity. No other explanation of these actions seems

possible unless it is assumed that calcium produces a general sedative action on neuromuscular excitability thus giving slowing of the heart-rate and cessation of gastric activity.

7. Prostigmin strongly stimulates the fasting gastric movements but slows the action of the heart. These findings were constant but they were not in agreement with the previous work done by Veach, Lauer and James.(1938) No alteration of this action was produced by premedication with atropine.

8. Many authors have found that adrenaline has different effects with varying dosage. My own observations show that in most cases adrenaline has a sedative influence on gastric activity, even when small doses are given. Quickening of the pulse occurs with the larger doses. Adrenaline is thus completely sympatheticomimetic in its action.

9. Strychnine has a stimulant action on the fasting contractions of the stomach. After a course of strychnine, the stomach empties more quickly than before. A single dose causes an increased secretion of fasting gastric juice. There is no evidence of a "tonic" action and the drug has no effect on the proportion of circulating white cells.

10. Morphine has a peculiar action on the gastric fasting contractions: it produces a period of rest followed by a phase of increased gastric activity; and then follows a period of complete quiescence. No conclusion can be drawn from this as to the advisability of using morphine in haematemesis for the conditions existing in haematemesis differ in many important particulars from those present during my experimental work; and the dose of morphine administered to patients with haematemesis is not comparable with the quantities which I used. The exaggeration of motor activity which occurs after morphine may account for the sickness which sometimes occurs after administration of this drug.

11. Histamine causes a cessation of gastric motor activity accompanied by an increase of gastric secretion. Larostidin has a sedative action on the movements of the stomach with no marked effect on gastric secretion. This finding is of some importance since little attention is paid in the literature to this apparent dissociation between the motor and secretomotor fibres of the autonomic nerve supply to a viscus.

APPENDIX

Effect of Strychnine

Case 1:

M.G., female, aged 35 years, admitted 11.1.39.

Complaint. A dull pain in right lumbar region was present of one week's duration. No previous serious illnesses had occurred.

Examination. Patient was afebrile and no abnormality was found on clinical examination.
B.P.120/60.

Urine. Pus cells were present.

Treatment. Urine was free from pus on 16.1.39, and the alkali given was stopped on 18.1.39.

Progress Notes.

18.1.39. Strychnine gr. 1/60 was started. This was given by hypodermic injection twice per day.

19.1.39. Patient was free from all symptoms and feeling well. Strychnine increased to gr.1/30, twice per day.

21.1.39. Appetite has been good. Patient has slept well. The strychnine injection increased to gr. 1/30 three times per day.

24.1.39. Knee-jerks appeared slightly exaggerated.

28.1.39. No change in condition noted. The exaggeration of the knee-jerks was not maintained. Strychnine administration stopped.

Total Strychnine given was 50 milligrams.

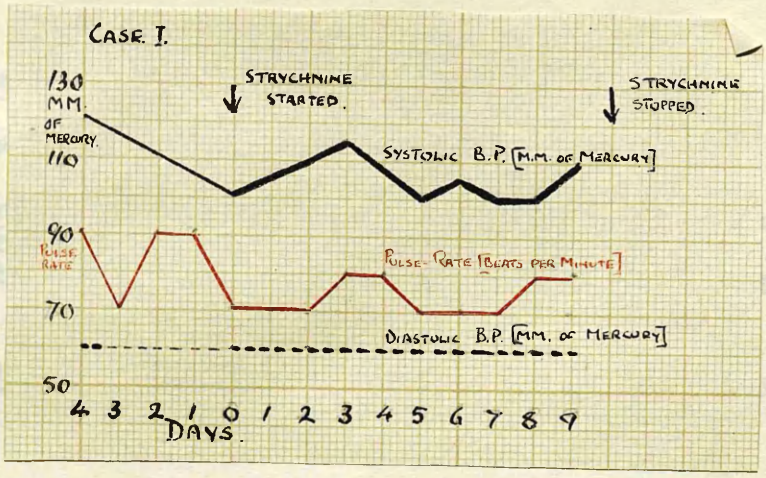

Figure 95.

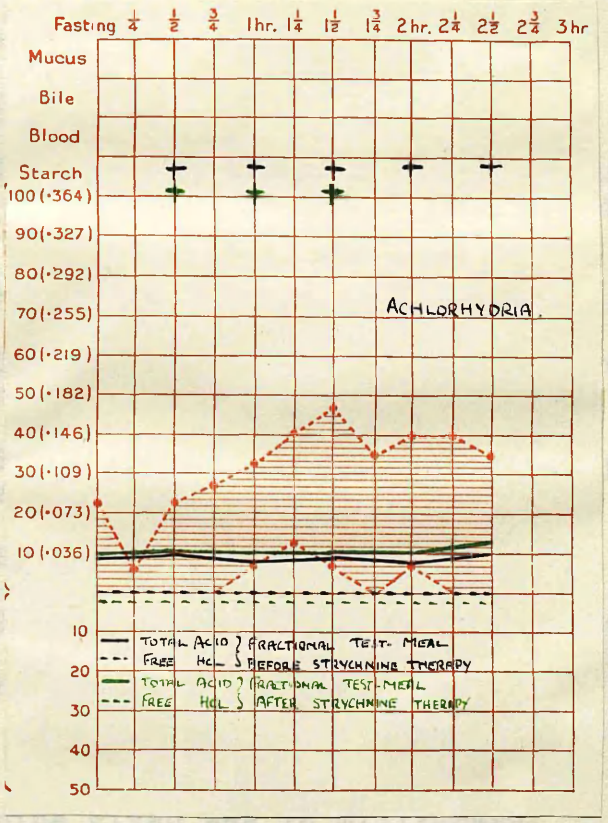

Figure 96.

The graph shows blood pressure and pulse-rate readings before and during strychnine therapy. (Figure 95). Fractional test-meals performed before and after strychnine are shown. (Figure 96).

Comment: Strychnine appeared to produce no noticeable change in patient's clinical condition. No alteration in blood-pressure or pulse-rate was found. The stomach emptied more quickly after the strychnine therapy.

Case 2:

T.M., male, aged 68 years, admitted 4.1.39.

Complaint. Epigastric pain occurring half an hour after food, of two years' duration. No vomiting. Appetite good. No previous serious illness. No history of loss of weight.

Examination. A thin, pale man, with badly decayed teeth. No other physical abnormality was found.
B.P. 186/96.

X-ray. The stomach and duodenum showed no abnormality.

Urine. Normal.

Progress Notes.

17.1.39. No pain has occurred since admission to hospital. No abnormality was detected on repeated abdominal examination.

4.2.39. No change was noted in condition.

6.2.39. Strychnine gr. 1/60 given three times per day by injection was started.

10.2.39. Strychnine gr. 1/30 three times per day subcutaneously now given.

20.2.39. No change was found in patient's condition.

25.2.39. Strychnine administration was now stopped.

6.3.39. No change was noted.

Total Strychnine given was 72 milligrams.

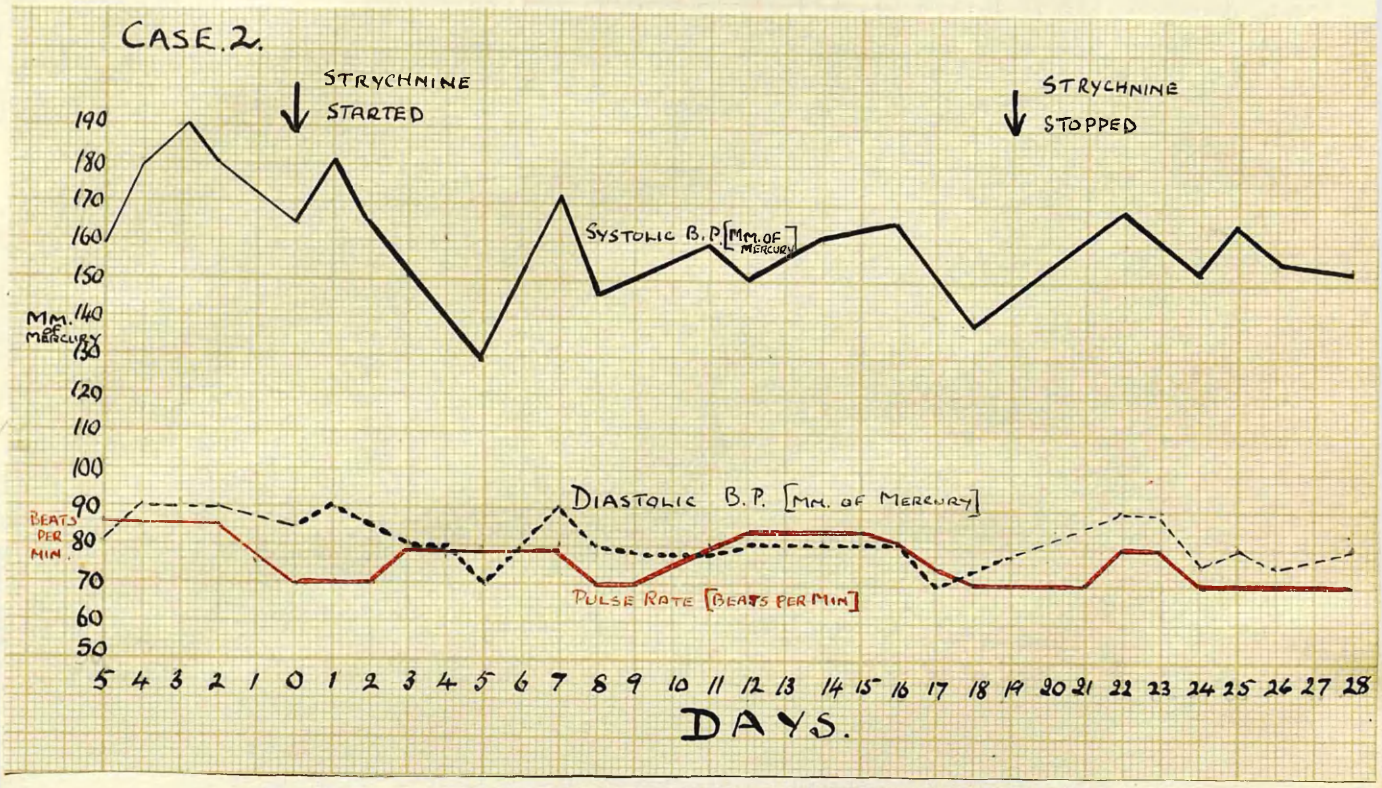

Figure 97.

The graph shows blood-pressure and pulse-rate readings before and during the administration of strychnine (Figure 97). Fractional test-meal charts performed before and after strychnine are seen. (Figure 98). A blood sugar curve (oral) was done before strychnine therapy was started and another after it was finished and the two are shown compared. (Figure 99).

Comment: No change was found in blood-pressure, pulse-rate or patient's clinical condition. The test-meals show a slightly more rapid emptying of the stomach after strychnine. The blood sugar curves both of which were normal showed no change. The type of curve in each was identical.

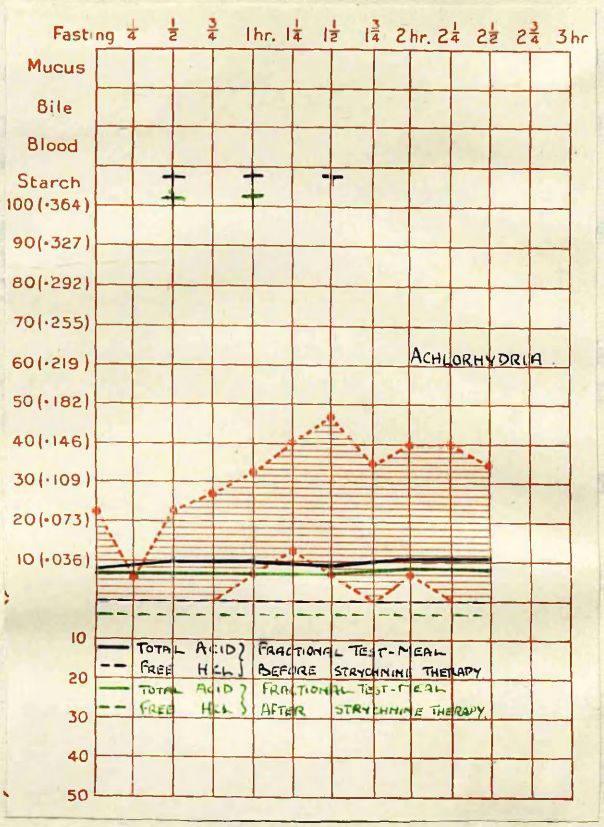

Figure 98.

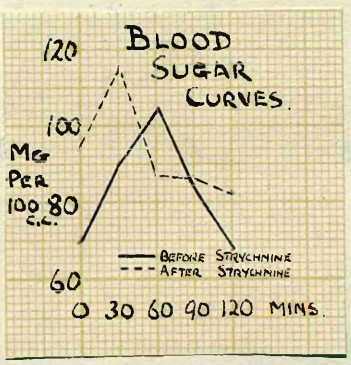

Figure 99.

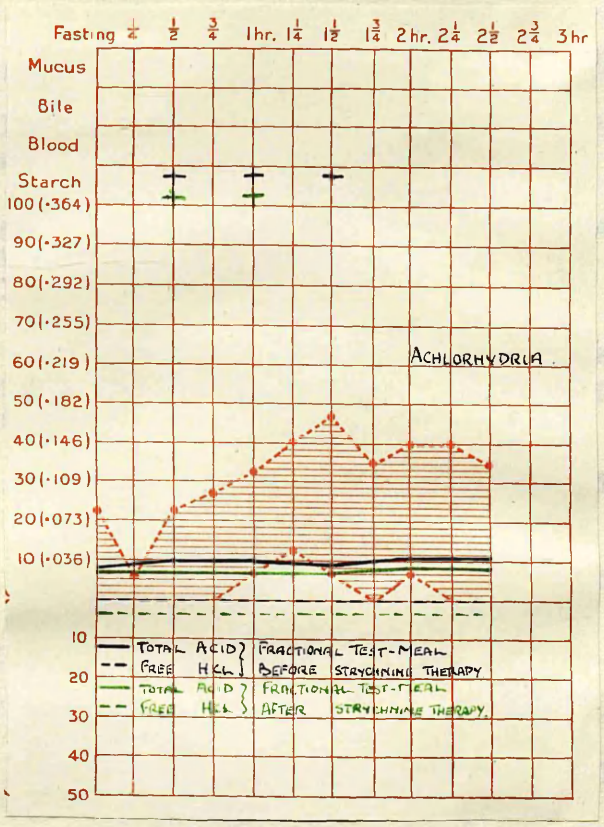

Figure 98.

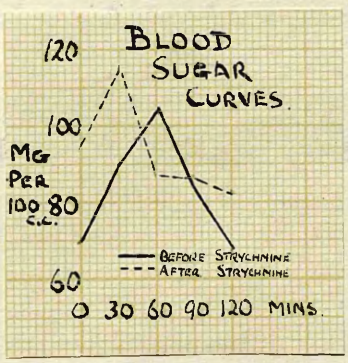

Figure 99.

Case 3:

P.G., female, aged 44 years, admitted 10.5.39.

Complaint. Intermittent attacks of dull pain in the left flank have occurred over a period of one month. These last about ten minutes. Twelve years ago, floating kidney was diagnosed and for the next two and a half years she wore an abdominal belt.

Examination. No physical abnormality was detected. The patient was of an introspective type. B.P. 110/70. Hb. 80% (Sahli).

X-ray. The stomach, duodenum, colon and urinary tract showed no evidence of disease.

Urine. No abnormal constituent was detected.

Progress Notes.

18.5.39. Patient was well, no complaints.

31.5.39. Strychnine gr. 1/30 hypodermically was started twice per day.

2.6.39. The dose increased to gr. 1/30 three times per day.

14.6.39. No change noted in condition.

17.6.39. Strychnine reduced to gr.1/30 twice per day.

22.6.39. Strychnine stopped.

Total Strychnine given was 100 milligrams.

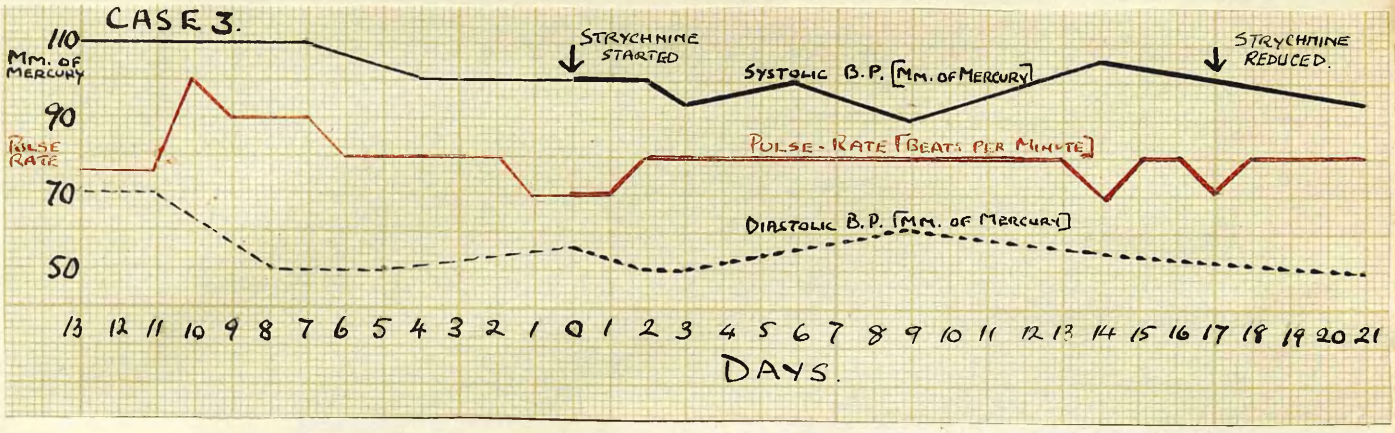

Figure 100.

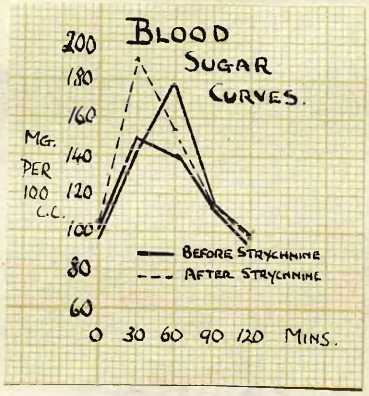

Figure 101.

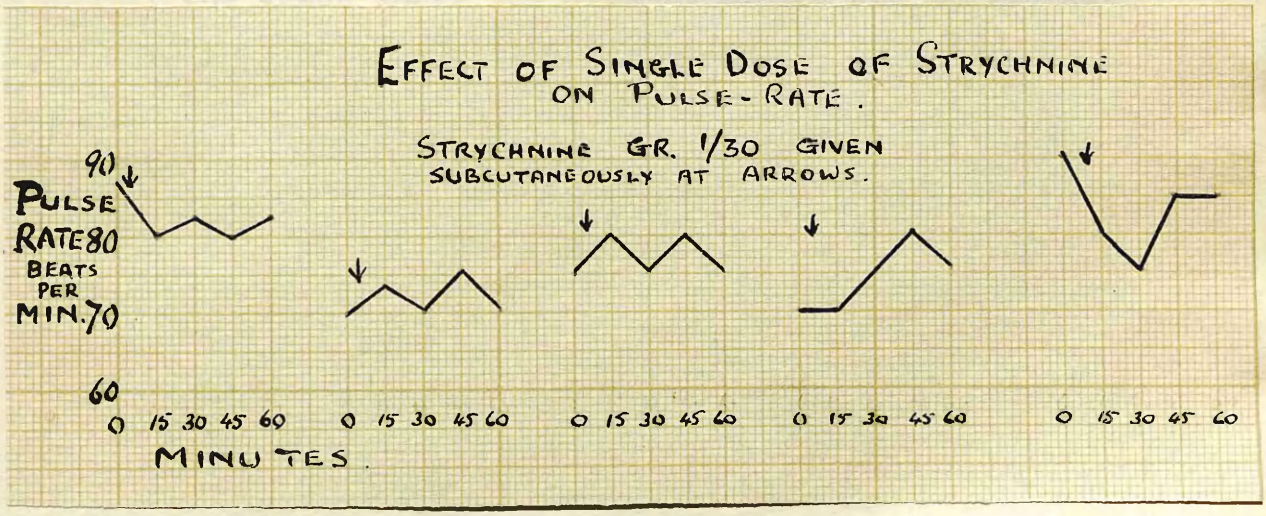

Figure 102.

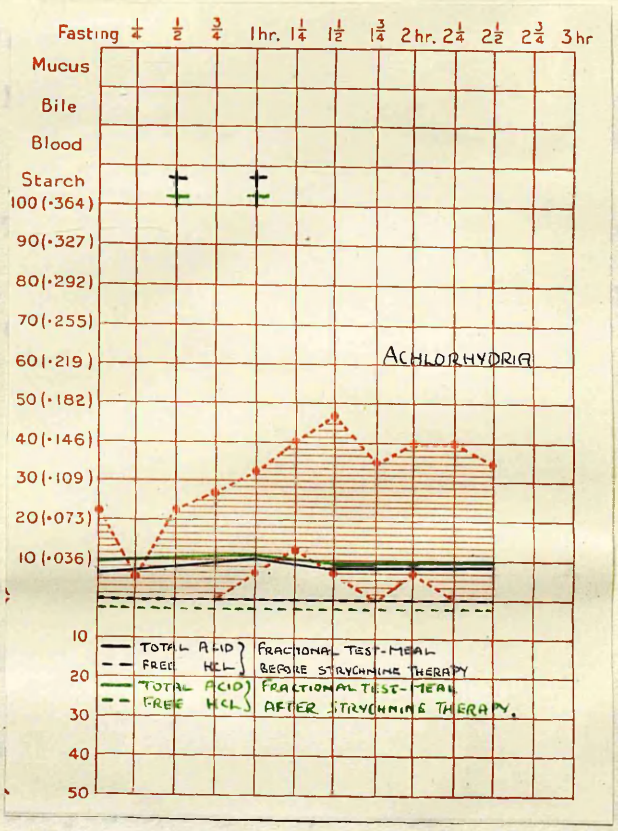

Figure 103.

The graph shows the blood-pressure and pulse-rate readings before and during strychnine treatment (Figure 100). Fractional test-meals were performed before and after strychnine. (Figure 103). Two blood sugar oral curves were done one before and one after strychnine therapy. (Figure 101). On ten occasions the pulse-rate was followed at fifteen minute intervals until one hour after the injection. (Figure 102).

Comment: No significant change in the pulse-rate readings, blood-pressure or patient's clinical condition was noted. The blood sugar curves, all normal, demonstrated that the strychnine was apparently without effect as regards glucose metabolism.

Case 4:

D.F., female, aged 59 years, admitted 9.1.39.

Complaint. Loss of appetite and weakness for three months. No past history of serious illness.

Examination. A thin woman with dark circles round her eyes. The arteries were easily palpable at the wrists. The heart did not appear to be enlarged and the sounds were of good quality with systolic murmur at the apex, not conducted. The other systems revealed no evidence of disease.

Urine. Normal.

Blood Urea. 40 mgm. per 100 c.c.

X-ray. Barium meal and enema revealed no evidence of disease.

Progress Notes.

25.1.39. Patient felt much better, now no complaint - treatment, rest in bed.

30.1.39. Strychnine gr. 1/60 hypodermically twice per day was started.

31.1.39. The dose increased to gr. 1/30 twice per day.

1.2.39. A further increase to gr. 1/30 three times per day.

3.2.39. Patient stated appetite was better.

13.2.39. No change in condition.

15.2.39. Strychnine therapy stopped.

1.3.39. No change noted.

Total Strychnine given was 90 milligrams.

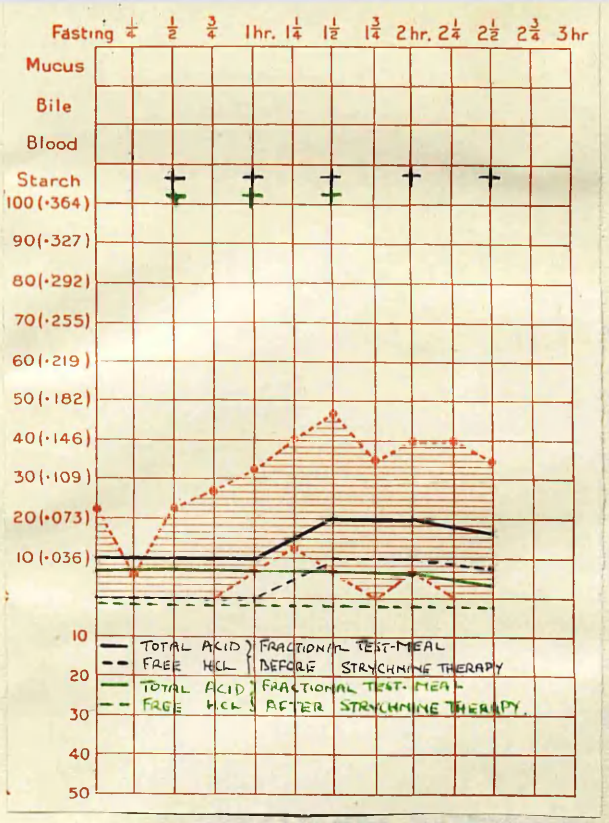

Figure 106.

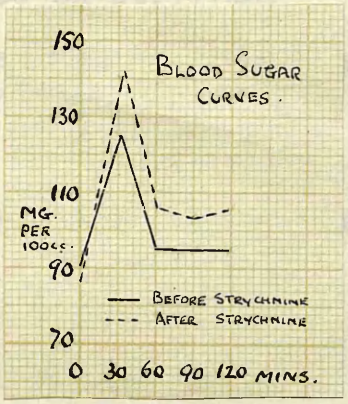

Figure 105.

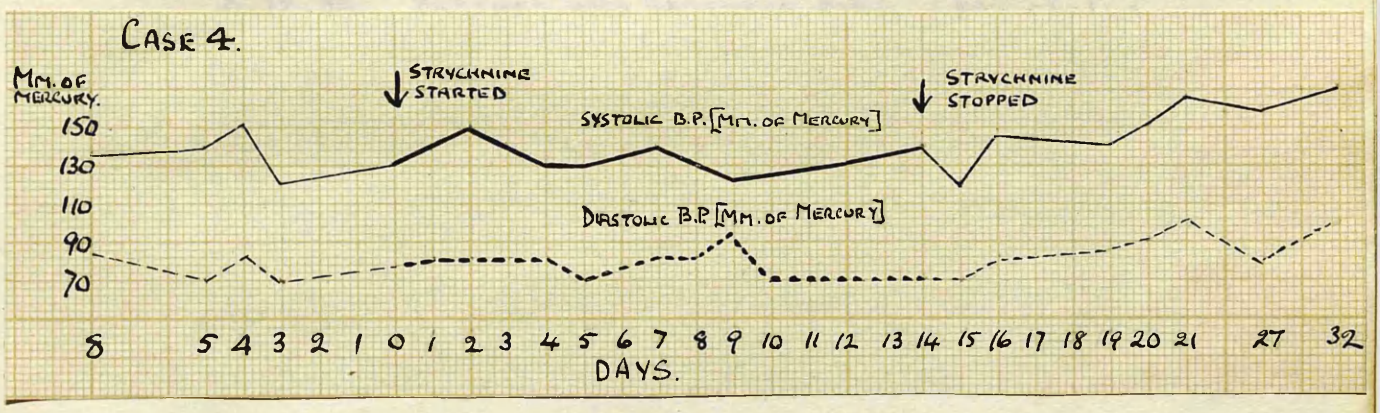

Figure 104.

The blood-pressure, pulse-rate readings and blood sugar curves. (Figures 104, 105) Test-meal charts before and after strychnine therapy. (Figure 106).

Comment: No change noted in blood-pressure, pulse-rate readings, blood sugar curves or patient's clinical condition. The stomach shows an absence of free hydrochloric acid after the strychnine and it empties more rapidly after the injections. The patient's weight was less by 1 lb. after the course of treatment with strychnine, notwithstanding her statement that her appetite had improved.

Case 5:

E.D., female, aged 23 years, admitted on 14.11.38.

Complaint. Attacks of breathlessness and coughing have been troublesome for past three weeks. She was employed at a fishmonger's and she did not like her work.

Examination. Physical examination revealed no abnormality. B.P. 115/60.

X-ray. No evidence of disease in chest.

Urine. Routine tests showed no abnormality.

Progress Notes. While in hospital the patient had two nocturnal attacks of breathlessness. These passed off without treatment in less than ten minutes.

5.12.38. Patient now appeared well. Strychnine gr. 1/60 hypodermically given twice per day.

6.12.38. Dose was increased to gr. 1/60 three times per day.

7.12.38. A further increase to gr. 1/30 twice per day was made.

22.12.38. No change in condition was noted.

23.12.38. Strychnine therapy stopped.

Total Strychnine given was 70 milligrams.

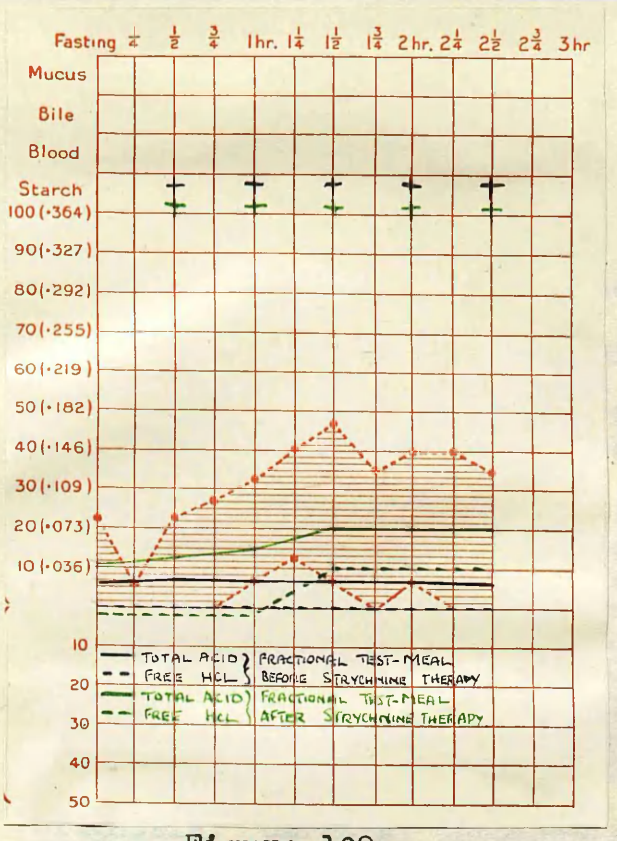

Figure 108.

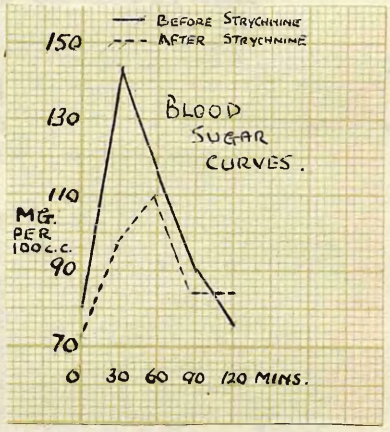

Figure 109.

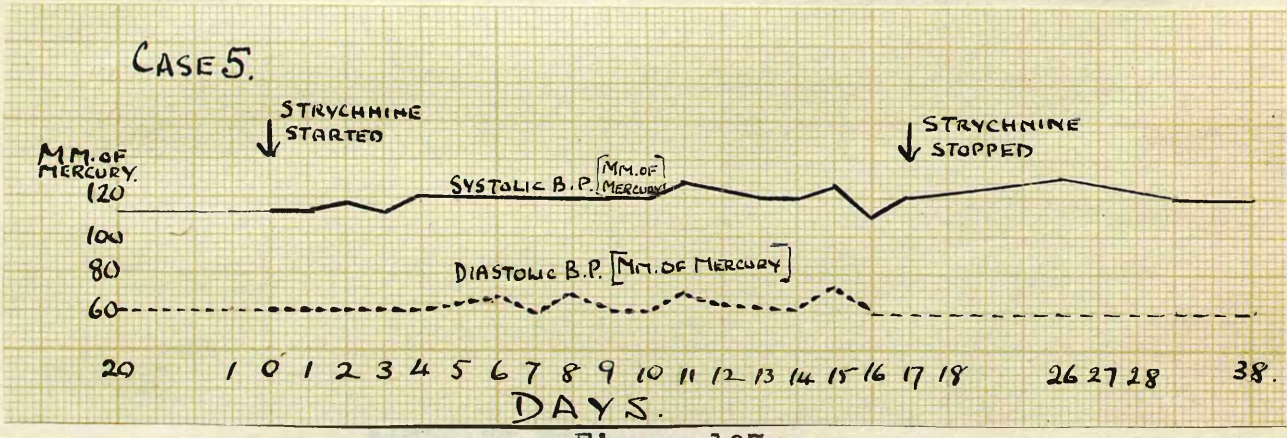

Figure 107.

Blood-pressure readings before, during and after strychnine therapy. (Figure 107) Test-meal charts and blood sugar curves also taken before and after treatment. (Figures 108, 109).

Comment: No change in patient's general condition or in the blood-pressure readings was noted. Some free hydrochloric acid appeared in the test-meal after strychnine. No change was found in the emptying time. In comparing the blood sugar curves, a discrepancy was noted in the first hour of the second curve. It appeared likely that in this case the peak of the rise was missed in the withdrawal of the sample.

Case 6:

J.D., female, aged 40 years, admitted on 16.11.38.

Complaint. Difficulty in walking of four months' duration. A feeling of flushing and tingling was felt in the right leg. No sphincter trouble has been experienced. No previous serious illnesses had occurred.

Examination. C.N.S. The pupils were equal, reacting normally to light and accommodation. The left arm and left leg reflexes were exaggerated. The right plantar response was extensor, the left flexor. The grip in the right hand was much weaker than in the left. When the patient walked the right leg was dragging. No abnormality in sensation beyond some loss of vibration sense in both ankles. B.P. 190/90. Other systems showed no abnormality.

Diagnosis. Cerebral thrombosis.

X-ray. No evidence of disease in skull, or stomach was seen.

Urine. No abnormal constituent was found.

Wasserman Reaction (Blood). Negative.

Progress Notes.

3.1.39. Patient was brighter and feeling better.

6.1.39. Headaches were troublesome.

12.1.39. Sweating was severe and patient was not sleeping well.

18.1.39. Condition unchanged, strychnine gr. 1/60 given twice per day.

20.1.39. Dose increased to gr.1/60 three times per day.

25.1.39. Signs were unchanged, sweating still persisting.

30.1.39. Strychnine dose increased to gr. 1/30 twice per day.

2.2.39. Sweating still was troublesome - no change in clinical condition.

14.2.39. Strychnine was stopped.

8.3.39. Patient was in much the same condition - weakness of right arm and leg still present.

Total Strychnine given was 100 milligrams.

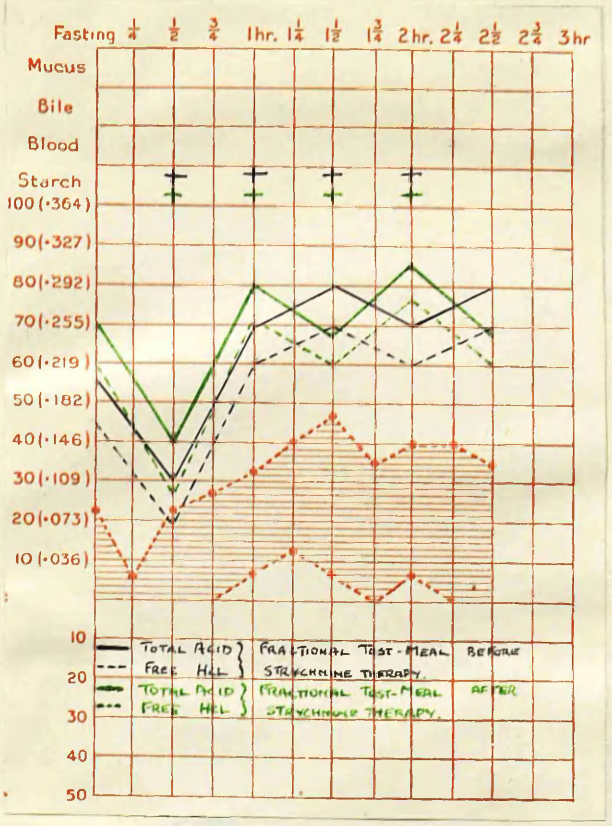

Figure 111.

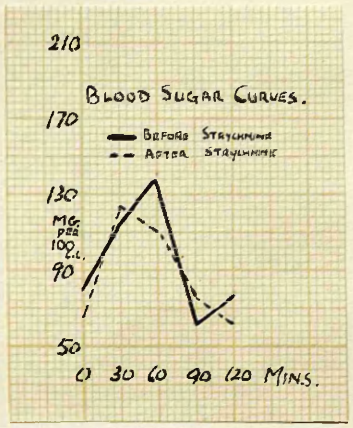

Figure 112.

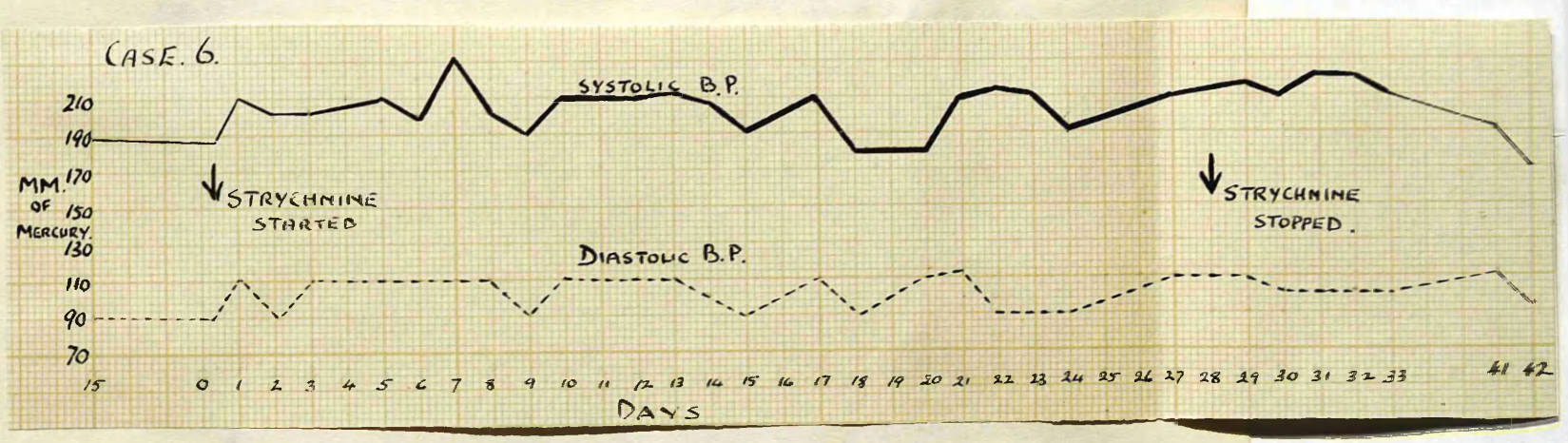

Figure 110.

Graphs of blood-pressure readings and test-meal charts. (Figures 110, 111). Blood sugar curves before and after strychnine. (Figure 112).

Comment: No clinical improvement while under strychnine therapy found. No change in the weakness of the arm or leg was noted and the blood-pressure graph, blood sugar curves and test-meal charts are likewise unaltered.

Case 7:

S.B., female, aged 27 years, admitted on 16.2.39.

Complaint. Fainting turns for the past five years. Pains in the legs and ankles recently.

Examination. The patient was of a highly neurotic disposition worrying over trivial details. No abnormality on physical examination was detected. B.P. 90/40.

Urine. No abnormal constituent was present.

Blood Sodium 304.6 mgm. per 100 c.c.

Wasserman Reaction (Blood). Negative.

Progress Notes.

1.3.39. Patient felt very well, strychnine gr. 1/60 by hypodermic injection given twice per day.
2.3.39. Strychnine increased to gr. 1/30 twice per day.
3.3.39. The patient stated she was not sleeping well. The dose was increased to gr.1/30 three times per day.
7.3.39. The patient felt that she was sleeping all the time and that her appetite was not as good as before.
13.3.39. A dull headache was present and a fainting attack occurred this evening.
15.3.39. Sore throat developed. Strychnine stopped.

Total Strychnine given was 78 milligrams.

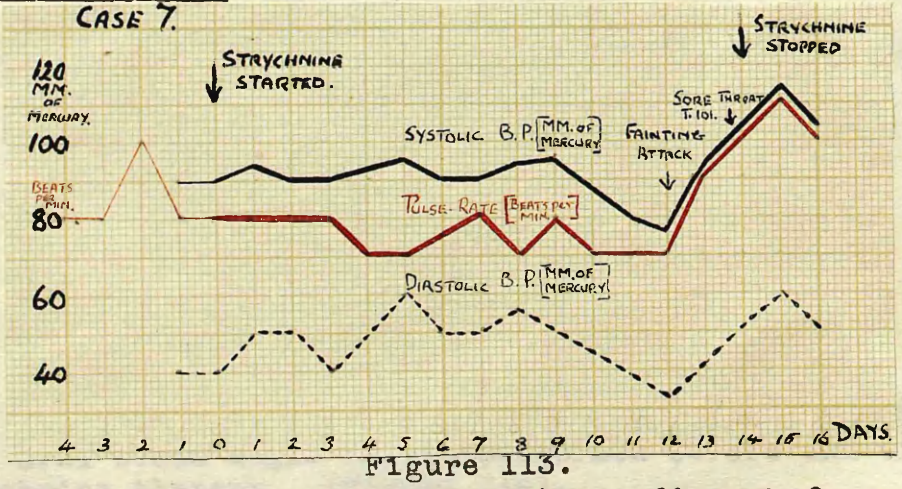

Figure 113.

Blood-pressure and pulse-rate readings before, during and after course of strychnine. (Figure 113).

Comment: The patient had a low blood-pressure, and was a very suitable type clinically for a tonic. No change in clinical condition and no raising of the blood-pressure was noted after the strychnine therapy.

Case 8:

J.C., female, aged 38 years, admitted on 20.12.38.

Complaint. Pain in the left side of the chest with persistent headache and cough of two days' duration.

Examination. A pale, thin woman was seen with a slightly impaired percussion note at both bases of the lungs. No adventitiae were present and no other abnormality was found on physical examination. B.P. 90/50.

X-ray. No evidence of disease present in chest.

Urine. Normal.

Progress Notes.

6.1.39. The chest was clear to physical examination.
7.1.39. Strychine gr. 1/60 hypodermically was given twice per day.
9.1.39. The strychnine dosage increased to gr. 1/30 twice per day. The patient was feeling very well.
10.1.39. The dose again increased to gr. 1/30 three times per day.
12.1.39. The patient was sleeping well and thought her appetite had increased. No change noted in reflexes.
14.1.39. Strychnine therapy was stopped.

Total Strychnine given was 26 milligrams.

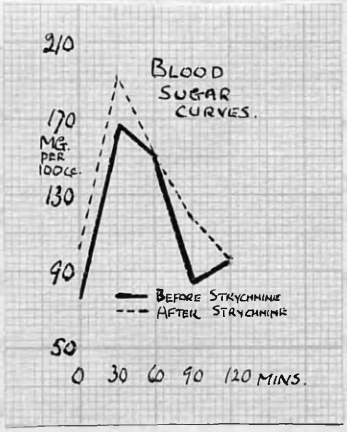

Figure 114.

Oral blood sugar curves performed before and after strychnine therapy. (Figure 114).

Comment: No change in clinical condition, no alteration in oral glucose curve was noted. Weight practically unchanged. (Weight before strychnine 7 st. 2½ lbs., after 7 st. 2 lbs.)

Case 9:

A.H., female, aged 53 years, admitted on 2.2.39.

Complaint. Pain present on micturition and also in the lumbar region. No frequency of micturition had been noted and the urine appeared to be of normal colour. The appetite was poor.

Examination. No physical abnormality was detected beyond numerous extrasystoles. B.P. 120/70.

Urine. No abnormal constituent was found and no growth of organisms was obtained.

Progress Notes:

4.2.39. Alkaline mixture was started.

2.3.39. Alkaline mixture stopped. Patient had no complaint, strychnine gr. 1/60 twice per day started.

3.3.39. The dose was increased to gr. 1/30 twice per day.

6.3.39. Again increased to gr. 1/30 three times per day.

9.3.39. No change in condition noted. Extrasystoles were still heard at the apex.

14.3.39. No change in reflexes or general condition.

15.3.39. Strychnine reduced to gr. 1/30 twice per day.

16.3.39. No extrasystoles heard to-day. No exaggeration of reflexes and no change in general condition.

20.3.39. Extrasystoles present again to-day.

23.3.39. The strychnine administration stopped.

24.3.39. No extrasystoles found.

8.4.39. Patient showed extrasystoles occurring every 4th.beat. No change in clinical condition was found.

Total Strychnine given was 100 milligrams.

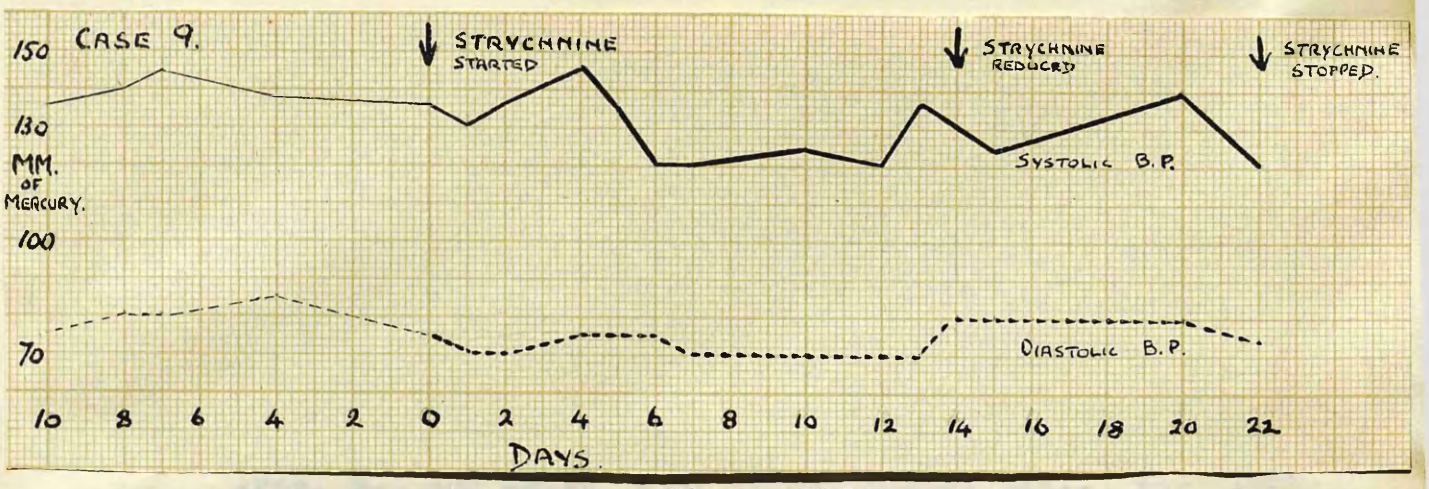

Figure 115.

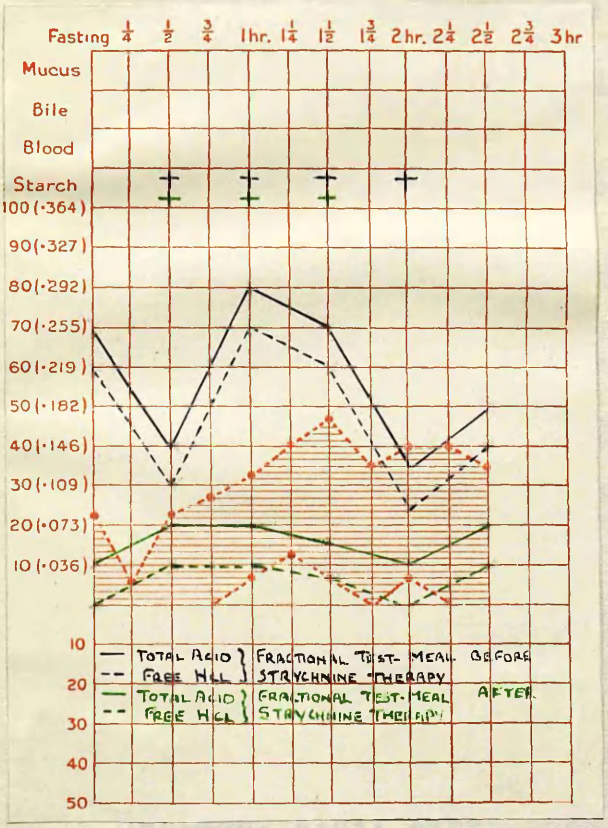

Figure 116.

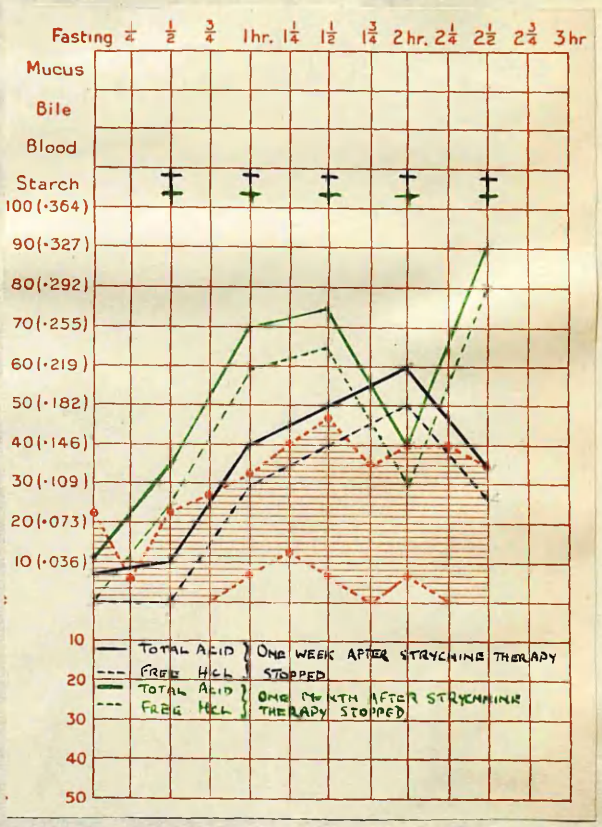

Figure 117.

Blood-pressure readings before and after strychnine. (Figure 115).

Comment: The patient's condition and blood-pressure were unaltered by the strychnine. The test-meal results showed an increased rate of emptying with a lower curve of free hydrochloric acid, after the injections. (Figure 116). Other fractional meals, one week and one month after the post-strychnine meal, showed a closer approach to the original curve. (Figure 117).

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