THE CONTRACTILE MECHANISM OF THE GALL-BLADDER AND ITS EXTRINSIC NERVOUS CONTROL[1].

By F. A. BAINBRIDGE and H. H. DALE.

(Eighteen Figures in Text.)

(*From the Physiological Laboratory, University College, London, and the Wellcome Physiological Research Laboratories, Herne Hill.*)

Introduction. The experiments here recorded were undertaken as a preliminary to a general consideration of the causes which lead to the pouring of bile into the duodenum at the stage of digestion when its presence is required. The investigation has proved more complicated than was anticipated; and it seems better to communicate at once our observations on the contractile mechanism of the gall-bladder, reserving for future discussion experiments on the actual process of secretion.

Methods. All the experiments were made on dogs, fully anæsthetised with the A. C. E. mixture, after a preliminary dose of $\frac{1}{2}$—1 gr. of morphine. Direct observation of the contractions of the gall-bladder was found to be impossible, the movements being too slow to be accurately followed. Various methods of mechanical recording were, therefore, given a trial. To the obvious method of inserting a cannula into the common duct and connecting with a water-manometer there are two fatal objections: it is impossible to be certain that nerves coursing up the duct to the bladder are not injured; and the presence of valves in the common duct makes it impossible to refill the bladder when once it has emptied itself, so that a relaxation cannot be recorded. The record so obtained, in fact, is merely that of the maximum pressure exerted by the gall-bladder during the experiment. An attempt was made to avoid these difficulties by passing a small gum elastic catheter up the common duct into the gall-bladder: but, in this case, the viscosity of the bile and the necessarily narrow bore of the catheter formed a combination fatal to an accurate record.

[1] The expenses of this research were in part defrayed by grants from the Government Grants Committee of the Royal Society, and the Scientific Grants Committee of the British Medical Association.

The following method which we ultimately adopted, and found in most ways quite satisfactory, is that devised by Doyon[1], with modification in details. A thin balloon of india-rubber is tied over the end of a gum elastic catheter, about 1 inch of the catheter being inside the balloon. The catheter is connected by a length of small-bore india-rubber tubing with a wide glass reservoir half filled with water, and usually at a height of about 15 cm. above that of the gall-bladder. The upper end of this reservoir is connected by rubber-tubing with a small Hürthle piston-recorder. The balloon is inserted in the deflated condition through a small cut made in the fundus of the gall-bladder, tied in, and then filled with warm water from the reservoir.

In our earlier experiments the abdominal wound was closed. Under such conditions several evident sources of error presented themselves. Variations of external pressure to which the gall-bladder yields passively are registered by the recorder and may be quite indistinguishable from the effects of active contraction of the muscular wall of the bladder itself. Such variations may be caused by:—

(1) Varying contraction of the abdominal walls and diaphragm.

(2) Activity of contiguous contractile viscera.

(3) Changes in volume and turgescence of the liver substance, with which the gall-bladder is frequently in contact over the greater part of its surface.

These difficulties were met as follows:—

(1) The animal was either fully curarised, or the chest was opened, the phrenic nerves cut and the diaphragm divided according to a method to be described later. The abdominal walls were widely opened by a crucial incision and the flaps held back by weighted hooks, the gall-bladder being protected from cold and evaporation by frequently renewed flannels soaked in warm saline, or by immersing the animal in a warm saline bath. If insufficient attention be given to this protection against cooling it is very easy, when the sympathetic nerve-supply is stimulated, and especially when adrenalin is the mode of stimulation, to produce an effect of simple hyperæmia of the gall-bladder muscle, which will be described later.

(2) Care was taken to prevent contact with contractile viscera by drawing these aside with hooks and screening the gall-bladder with sponges and flannels. These measures, however, were merely precautionary, since the danger of disturbance from this cause is but slight

[1] Doyon, *Archives de Physiol.* xxv. p. 678. 1893.

when the abdominal walls are freely opened. We have, in fact, deliberately allowed contact between a vigorously contracting stomach and the gall-bladder, under such conditions, without being able to detect any indication of the contractions upon the gall-bladder record.

(3) Upon the effect of changes in the volume of the liver we intend to lay some stress, as it has been completely left out of consideration in earlier investigations. We found it essential to eliminate this influence either by separating the gall-bladder from the liver, or by a dissection which gave the liver perfect freedom of expansion.

Another precaution taken was the registration of the blood-pressure simultaneously with the contractions of the gall-bladder. This is omitted in the tracings unless there is special reason for giving it.

I. SPONTANEOUS CONTRACTIONS.

A record of the volume of the gall-bladder, obtained as above described, shows spontaneous variations, which occur rhythmically at the rate of 1 to 3 per minute (Fig. 1); though noticeable even at the beginning of an experiment, this rhythm is usually more obvious after section of the splanchnic nerves, and still more so after the injection of

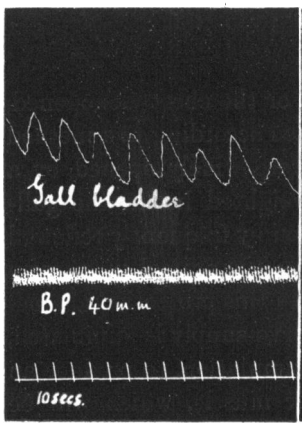


Fig. 1.

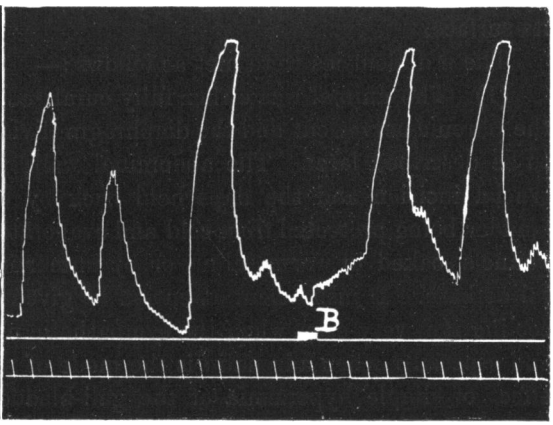


Fig. 2.

Fig. 1. × 1/7. To show the intrinsic rhythm of the gall-bladder. The animal was under curare, the gall-bladder separated from the liver. Vagi and splanchnics cut.

Fig. 2. × 1/7. Curare. Vagi and left splanchnic cut. Pressure on balloon in gall-bladder raised to 50 cm. of water, the exaggerated rhythm resulting. Right splanchnic cut at *B*, section causing momentary inhibition of rhythm. The *small* undulations in this and succeeding tracings were produced by the artificial respiration.

chrysotoxin. It is as well developed when the gall-bladder has been separated from the liver as when it is left in its natural relations, and it is clear that the undulations in question represent a genuine rhythmic contraction and relaxation of the gall-bladder muscle itself. On this point our experience is merely confirmatory of that of Doyon[1], who further detected a similar rhythmic activity in the gall-bladder even after its complete removal from the body.

Occasionally, but not always, we found that raising the water reservoir, and thereby subjecting the gall-bladder to an excessive distending force, produced great exaggeration of this rhythm, so that the record gave the picture of a series of violent contractions alternating with deep relaxations (Fig. 2). Diminution of the pressure restored the normal slight rhythm.

II. SYMPATHETIC NERVOUS SUPPLY.

Heidenhain[2] found that stimulation of the splanchnic nerves caused an initial increase in the flow of bile, followed by a diminution. He attributed the increase to contraction of the gall-bladder and bile passages.

Langley[3] found, on the other hand, that intravenous injection of supra-renal extract caused an increased flow of bile, which was preceded by a brief phase of slowing if the gall-bladder was not excluded by a clip. He suggested that the extract probably caused a relaxation of the gall-bladder tone.

The only direct observations made until recently, of the effect on the gall-bladder of stimulating the splanchnic nerves, are those of Doyon[4]. Using the balloon method of recording, with the apparatus arranged for recording changes of pressure rather than of capacity, he described a prolonged, slow contraction of the gall-bladder as the result of stimulating either splanchnic nerve. With adrenalin he subsequently obtained a similar effect.

A paper recently published by Freese[5] also gives an account of the nervous control of the gall-bladder. He appears to have confined his attention to the splanchnics, and obtained varying results—motor,

[1] Doyon, *Arch. de Physiol.* xxv. pp. 678, 710. 1893.

[2] Heidenhain, *Stud. d. Phys. Instit. z. Breslau.* Parts II and IV. p. 227. 1861—1868.

[3] Langley. This *Journal*, XXVII. p. 237. 1901.

[4] Doyon, *loc. cit.*, and *Arch. de Physiol.* XXVI. p. 19. 1894.

[5] Freese, *Bulletin*, Johns Hopkins Hospital. June, 1905.

inhibitory, or polyphasic, with a preponderance of motor effects—very similar to those described below as obtained in our own earlier experiments. He concludes that the splanchnics contain both motor and inhibitory fibres for the gall-bladder, deciding that the motor effect is genuine on the ground that it can be obtained after bleeding the animal to death.

Our own earlier experiments on the effect of stimulating the splanchnic nerves and of intravenous administration of adrenalin led to conflicting results. In some cases we obtained a result apparently identical with that of Doyon: in others we observed pure relaxation: in others again we found mixed effects, di- or even triphasic curves being

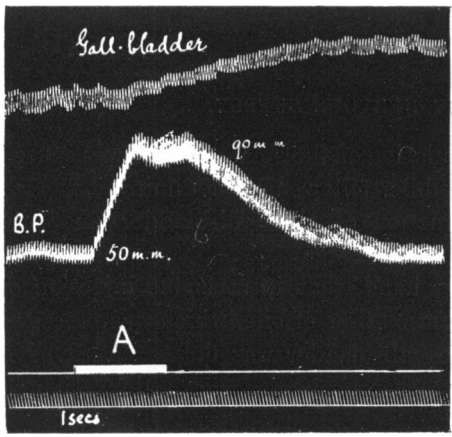


Fig. 3.

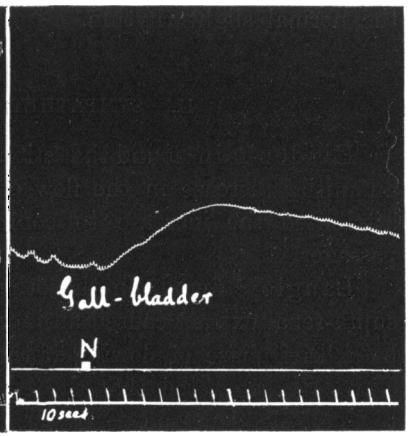


Fig. 4.

Fig. 3. $\times \frac{11}{18}$. Curare. Gall-bladder not separated from liver. Right splanchnic cut, the peripheral end being placed on Ludwig electrodes. Blood-pressure from carotid. At *A* stimulation of right splanchnic, coil at 3000 (Berne graduation).

Fig. 4. $\times \frac{11}{18}$. Curare. Gall-bladder not separated from liver. At *N* 4 c.c. 1 in 50,000 adrenalin chloride intravenously. Usual rise of blood-pressure.

produced. Figs. 3 and 4 show the apparently motor response to sympathetic stimulation often obtained when the gall-bladder is left *in situ*.

Thinking that this variety of result was due to the presence of at least two conflicting effects we attempted to determine which, if any, of these were due to extraneous causes, and which to intrinsic movements of the gall-bladder. We inserted between two adjacent lobes of the liver a balloon exactly similar to that in the gall-bladder and similarly con-

nected to a piston-recorder. This led to the discovery that the effects of apparent contraction observed in our tracings, and described by Doyon as the true and sole effect of stimulation of the sympathetic nerve-supply, were all produced equally well in the record taken from the control balloon. Whether the splanchnic nerves were faradised or adrenalin given intravenously this "artificial gall-bladder" always simulated contraction, even when the tracing from the gall-bladder itself indicated pure relaxation.

It was clear, therefore, that one of the effects complicating our records was the swelling of the liver which is caused by stimulation of the splanchnic nerves, and still more by the injection of adrenalin. The effect of stimulating the sympathetic nerve-supply was accordingly reinvestigated after removal of this complication as far as possible.

This was effected successfully by two methods. The first was the simple separation of the gall-bladder from the liver, down to the commencement of the cystic duct. This is easily performed by snipping through the peritoneal investment, where it passes from the liver on to the gall-bladder, inserting a finger into the opening thus made and gently tearing the gall-bladder away from its attachment. Although a small amount of liver substance always remains adherent to the gall-bladder, the bleeding is negligible. This method satisfactorily eliminates the effect of alteration in the liver volume, but irregular contractions of the diaphragm still complicate the tracing, and it is therefore necessary to give curare.

The second method obviated the use of curare and the handling of the gall-bladder in separating it from its attachments. Its principle was to allow free expansion of the liver by destruction of the dome of diaphragm normally enclosing it and resisting its outward enlargement. The chest was opened by longitudinal division of the sternum, the tendon of the diaphragm slit down to the vena cava, and the diaphragmatic muscle paralysed by section of the phrenic nerves. The chest was held open by weighted hooks so that the halves of the diaphragm gaped widely apart, the liver fell back into the cavity of the thorax, and the gall-bladder was brought uppermost. The liver was thus given perfect freedom of expansion, and its swelling merely raised the gall-bladder as a whole to a slight degree.

By both these methods we obtained uniform results. Under normal conditions—that is, unless both the blood-pressure and the tone of the gall-bladder had fallen very low, as at the end of a long experiment—relaxation was the invariable result of faradising the right splanchnic

nerve or intravenous injection of adrenalin. Fig. 5 shows the effect of stimulating the right splanchnic after opening the chest wall and slitting the diaphragm. Stimulation of the left splanchnic under such conditions, if it produces any effect at all on the gall-bladder, merely causes a small gradual increase in tone and rhythmic activity, such as accompanies a rise of general blood-pressure from any cause (Fig. 6). In Figs. 7 and 8 is shown the effect of adrenalin with the chest wall and diaphragm intact, the difference produced by separating the gall-bladder from the liver being clearly exhibited. It will be seen that the relaxation, which in Fig. 7 appears as a mere preliminary dip in a curve giving the impression of a predominantly motor effect, is shown in Fig. 8 to be the essential feature of the response to adrenalin. The pressure exerted on the gall-bladder by the swelling of the liver is further illustrated in both figures by the record obtained from the "artificial gall-bladder," which simulates a contraction. Another feature of Figs. 5 and 8 has yet

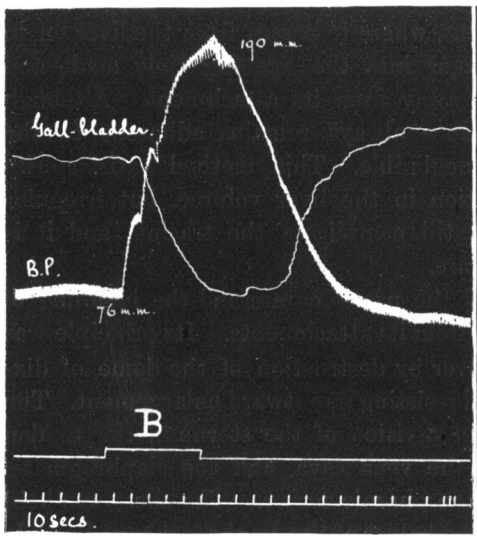


Fig. 5.

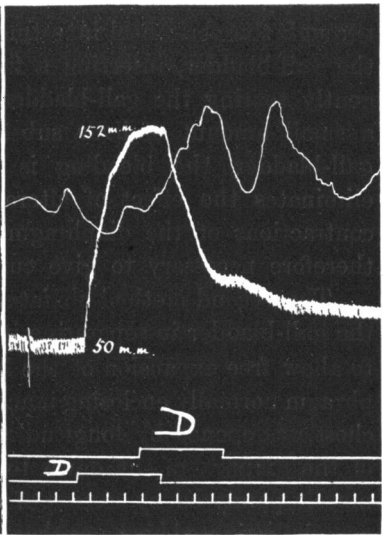


Fig. 6.

Fig. 5. $\times \frac{1}{10}$. Chest opened, diaphragm divided, phrenics cut. No curare. Right splanchnic dissected from the front, ligatured and cut above ligature. At *B* peripheral end of right splanchnic stimulated with coil at 10 cm.

Fig. 6. $\times \frac{1}{10}$. Conditions as in Fig. 5. Left splanchnic dissected from the front: at *D* the peripheral cut end of it stimulated with coil at 10 cm. The rise of b.-p. is accompanied by increase in tone of gall-bladder. (The point of the piston-lever not being opposite that of the manometer float, there are two signal lines: the upper for the gall-bladder, the lower for the blood-pressure.)

to be discussed. In both it can be seen that the record of the gall-bladder response to sympathetic stimulation shows, apart from the false effect of extraneous pressure, a true rise of tone, succeeding the inhibitory fall, and persisting for some time. It is probable that the improvement of blood-supply, caused by the greater permanence of the general than of the local effect of the sympathetic stimulation, is mainly responsible

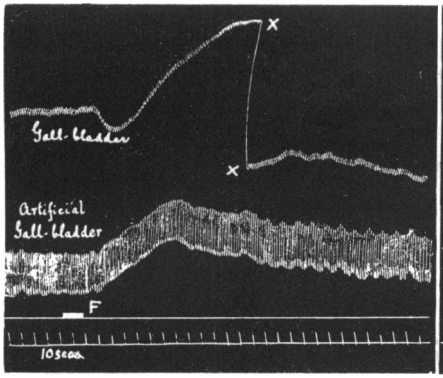


Fig. 7.

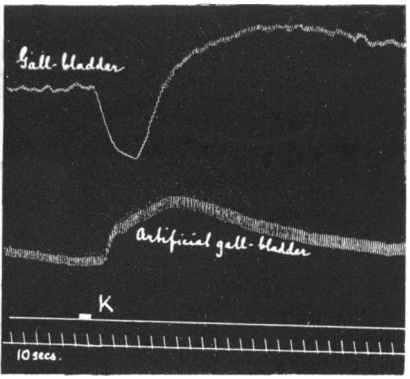


Fig. 8.

Fig. 7. × ⅓. Curare. Gall-bladder not separated from liver. "Artificial gall-bladder," between lobes of liver. Vagi and splanchnics cut. At *F* 4 c.c. 1 in 30,000 adrenalin chloride intravenously. Usual rise of blood-pressure. Between *X*—*X*, the lever of recorder having reached its limit, air was let out of recorder.

Fig. 8. × ⅓. From same experiment as Fig. 7, after separation of gall-bladder from liver. At *K* 6 c.c. of 1 in 30,000 adrenalin chloride intravenously. The usual rise of blood-pressure occurred.

for this. In harmony with this view is the greater prominence of this after-tone with adrenalin than with stimulation of the right splanchnic. The hyperæmia of the abdominal viscera, as the effect of an adrenalin injection wanes, is a well-known phenomenon. We have already mentioned the fact that stimulation of the left splanchnic, which we hold to be without direct effect upon the gall-bladder, produces a rise of its muscular tone, which we regard as an effect of the kind under discussion, due to the rise of general blood-pressure.

When the blood-pressure and the tone of the gall-bladder have both sunk to a low level, as at the end of a long experiment, we have several times observed a true increase of the tone of the gall-bladder in response to an injection of adrenalin. Fig. 9 shows such an effect. In this case the injection of adrenalin caused a permanent improvement in the blood-pressure, and to this we attribute at least the greater part of the

permanent improvement in the tone of the gall-bladder. A succeeding dose of adrenalin caused in this case a further rise of blood-pressure and a further increase in the tone of the gall-bladder. On the other hand, under conditions which allow the sympathetic stimulation to occur

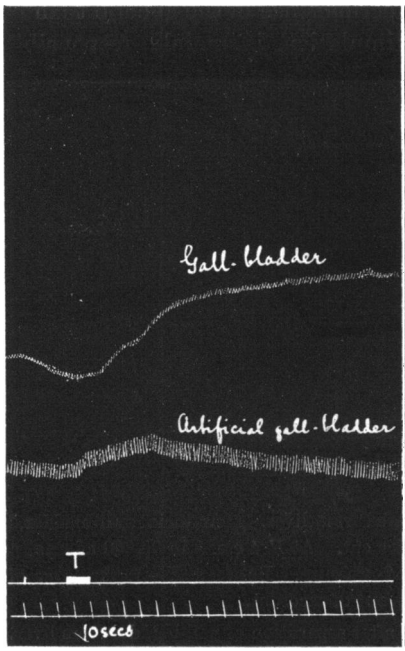


Fig. 9.

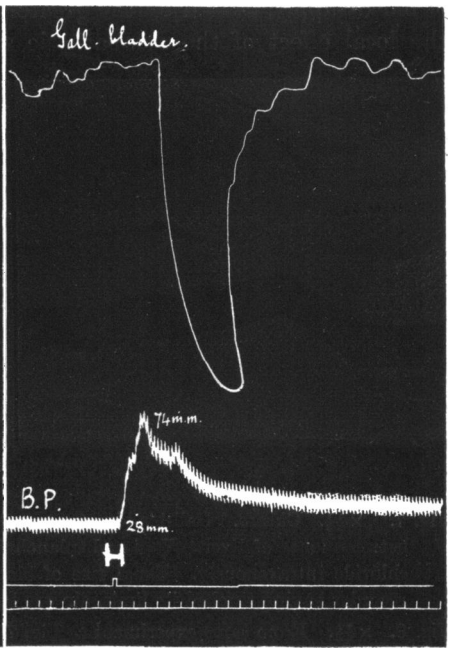


Fig. 10.

Fig. 9. $\times\frac{11}{18}$. Curare. Gall-bladder separated from liver. From the end of a long experiment. Blood-pressure had become very low (20 mm.); so had the tone of gall-bladder. At *T* 5 c.c. of 1 in 50,000 adrenalin intravenously.

Fig. 10. $\times\frac{11}{18}$. Chest opened, diaphragm divided, phrenics cut. No curare. Vagi and splanchnics cut. Blood-pressure from carotid. At *H* 1 c.c. 1 in 10,000 adrenalin intravenously.

without a large simultaneous rise of blood-pressure, the gall-bladder responds by pure relaxation without any after-tone. For example, the effect of adrenalin on the blood-pressure is greatly reduced by leaving the vagi intact, or when, as is often the case, the heart is weakened by the exposure entailed in opening the chest. Under either of these conditions we have obtained pure relaxation of the gall-bladder in response to adrenalin, without after-tone (Fig. 10). Again, when, by the administration of chrysotoxin[1], the endings of motor sympathetic fibres are

[1] Cf. Dale. *Proc. Physiol. Soc.* p. lviii. 1905. (This *Journal*, xxxii.)

paralysed, adrenalin produces practically no effect on the blood-pressure. Under these conditions the inhibition of the gall-bladder is very prolonged and quite uncomplicated by after-tone[1] (Fig. 11).

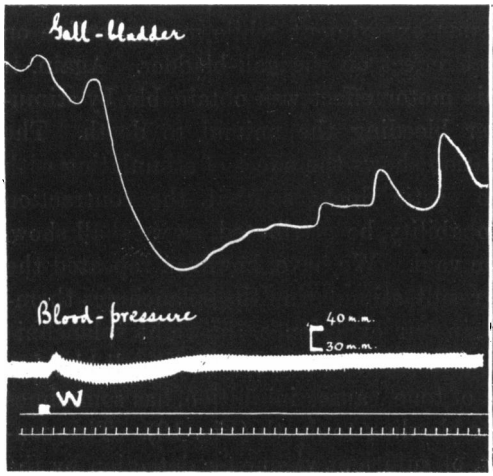


Fig. 11.

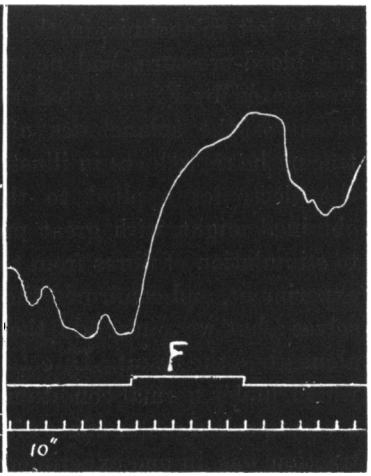


Fig. 12.

Fig. 11. $\times \frac{1}{10}$. From same experiment as Fig. 9, after intravenous injections of sodium chrysotoxin amounting to 0·2 gm. in all. At *W* 1 c.c. of 1 in 10,000 adrenalin intravenously.

Fig. 12. $\times \frac{1}{10}$. Conditions as in Fig. 5, but towards the end of an experiment, when animal was moribund, and blood-pressure very low (20 mm.). At *F* peripheral end of rt. splanchnic stimulated with coil at 8 cm. Blood-pressure rose to 40 mm.

When, however, due allowance has been made for the undoubtedly large part played by blood-pressure changes in producing these motor effects, and when, further, the simulation of motor effects by changes in liver-volume, which complicates the experiments of Doyon and of Freese, has been definitely excluded, there remains a small residuum of phenomena not satisfactorily accounted for. The difficulty, in fact, is not dissimilar to that met with by various observers in dealing with the effect of stimulating the splanchnics on the movements of the small intestine[2].

When the tone of the gall-bladder and the blood-pressure have both become low we have occasionally provoked a decided contraction by

[1] Here, however, the possibility must not be neglected of an admixture of motor fibres in the sympathetic supply to the gall-bladder. Chrysotoxin would paralyse these.

[2] Cf. Bunch. This *Journal*, XXII. p. 357, 1898, who gives the literature of the subject: also Bayliss and Starling. This *Journal*, XXIV. p. 99. 1899.

stimulating the right splanchnic nerve (Fig. 12). The possible effect of the rise of blood-pressure must be borne in mind, though in one such case exposure and cooling of the intestines had rendered this very small: but such a consideration will not account for the fact that stimulation of the left splanchnic, in the same experiment, while more effective on the blood-pressure, had no such effect on the gall-bladder. Again, it was stated by Freese that this motor effect was obtainable by stimulation of the splanchnics after bleeding the animal to death. The tracing he reproduces in illustration shows the effect of stimulating with the electrodes applied to the cystic duct; so that the contraction obtained might, with great probability, be attributed, as we shall show, to stimulation of fibres from the vagi. We have, however, repeated the experiment, and confirmed the result, stimulating the splanchnics themselves: but we must add that, in our experience, the right splanchnic alone gives the result. Direct application of adrenalin to the gall-bladder, which, under normal conditions of tone, causes inhibition, has sometimes a very marked motor effect after bleeding to death (Fig. 13). This contraction was, in one experiment, of sufficient vigour for detection by the

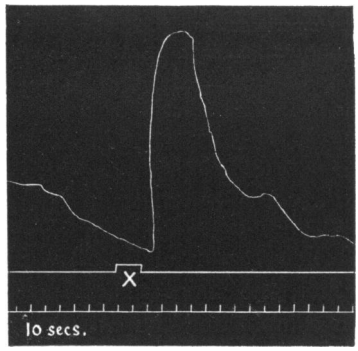


Fig. 13. $\times \frac{1}{2}$. Effect of directly applying adrenalin to gall-bladder of an animal bled to death. The solution used was 1 in 1000 pure adrenalin chloride, without preservative.

naked eye, and had the appearance of being limited to about one-fifth of the gall-bladder; the part affected being that adjoining the cystic duct. To this point we hope to give further investigation, and it will suffice now to point out that the conditions under which the result is obtained—complete anæmia, leading to intense inhibition of the fundus of the gall-bladder—are just those which would enable a localised motor effect to be recorded by the balloon or similar mechanical contrivance for registration. Whether the distribution be thus localised or not, we cannot

doubt that there is some admixture of motor fibres in the sympathetic nerve-supply to the gall-bladder. This, however, requires special conditions for its detection, and when the tone is maintained by an unimpaired circulation we find that inhibition is the invariable effect of exciting the sympathetic nerve-supply, and are disposed to attribute most of the motor effects described by previous observers to extraneous pressure. We find, further, that the sympathetic fibres to the gall-bladder run in the right splanchnic nerve only.

III. EFFECT OF THE VAGI.

Doyon[1] regarded the vagus as carrying only afferent impulses from the gall-bladder. On stimulating the central end of either vagus he observed inhibition of the gall-bladder tone. Presumably both the splanchnics were left intact. He obtained a similar result by stimulating the central end of either splanchnic when the other was intact.

Courtade and Guyon[2], accepting Doyon's account of the motor function of the splanchnics, examined the vagi for efferent fibres to the gall-bladder. Stimulating these nerves in the thorax they observed a motor response from the gall-bladder. They state that these motor fibres run in the gastric branches of the vagus, and claim to have traced them along the lesser curvature of the stomach to the cystic duct.

Our own experiments have been few in number, and have been confined to the confirmation of the motor effect of the vagus, without tracing the course of the fibres beyond the thorax. The effect is, in our experience, quite a small one and by no means easy to demonstrate. Stimulating the vagi peripherally in the neck, after a dose of atropine sufficient to abolish cardiac inhibition, we only once succeeded in producing an effect on the gall-bladder, and that merely a slight, though distinct and regularly produced augmentation of existent rhythmic contractions. Stimulation of the vagi intra-thoracically, even after section of the splanchnic nerves on both sides, gave no clear and unmistakable result unless chrysotoxin had been previously administered. It has been shown, in other connexions, that this drug, while not affecting sympathetic inhibitory nerve-endings to such an extent as to abolish the effect of adrenalin or of electrical stimulation, so far alters them as to block the normal tonic inhibitory impulses from the central nervous system or the ganglionic plexus, allowing stimulation of the cranial

[1] Doyon. *loc. cit.*

[2] Courtade and Guyon. *C. R. Soc. de Biol.* LVI. pp. 313 and 874. 1904.

autonomic supply to produce its full effect. The intestine, for example, after a large dose of chrysotoxin, responds more vigorously to stimulation of the vagus than it does after section of the splanchnic nerves only. We have found the same effect in the case of the gall-bladder. After a large dose of chrysotoxin (0·2 gram or more for a medium-sized dog),

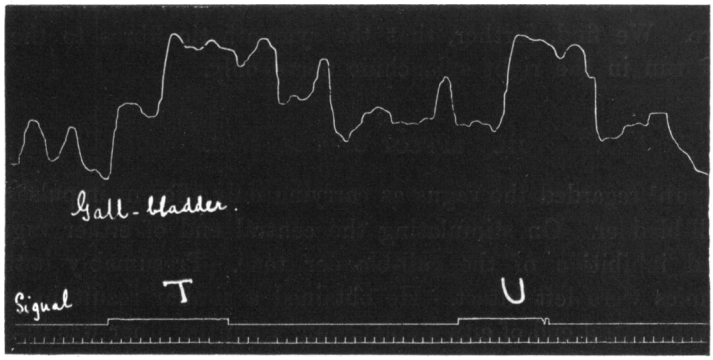
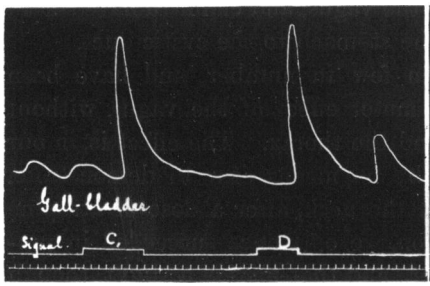


Fig. 14. × ½. From same experiment as Figs. 10 and 11. After 0·2 gm. chrysotoxin. At *T* and *U* peripheral end of left vagus stimulated in the thorax with coil at 6 and 5 cm. Blood-pressure unaffected.



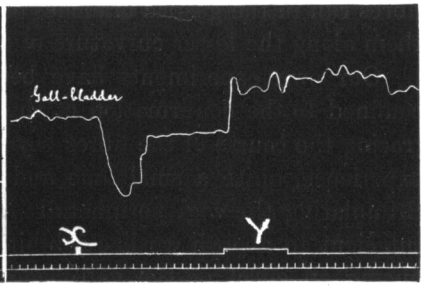


Fig. 15. Fig. 16.

Fig. 15. × 1/12. Conditions as in Fig. 14. At *C* and *D* the left vagus stimulated peripherally in the thorax, coil at 4 cm. Blood-pressure unaffected.

Fig. 16. × 1/12. Conditions as in Figs. 14 and 15, with less sensitive recorder. 0·2 gm. chrysotoxin given. At *X* 1 c.c. 1 in 10,000 adrenalin intravenously. At *Y* left vagus stimulated peripherally in the thorax: coil at 3 cm. The effects of sympathetic and vagus stimulation are contrasted.

stimulation of either vagus nerve in the thorax always causes a distinct augmentor effect on the gall-bladder, in which either increase of tone or exaggeration of rhythm may be the predominant feature, whilst in other cases, again, both may be simultaneously affected. In our experiments

the left vagus has always given a more marked effect than the right. (Figs. 14, 15, 16.)

IV. EFFECT OF VARIATION IN THE BLOOD-SUPPLY.

The stimulant effect on the gall-bladder muscle of hyperæmia has already been described in analysing the effects of injecting adrenalin into the circulation. As might be expected, the opposite holds good; anæmia produced by occlusion of the thoracic aorta causing a very marked inhibition, which affects the tone rather than the rhythmic activity of the muscle. The genuine nature of the effect is proved by obtaining it after separation of the gall-bladder from the liver (Fig. 15). The effect of anæmia corresponds therefore, in this as in other cases, to

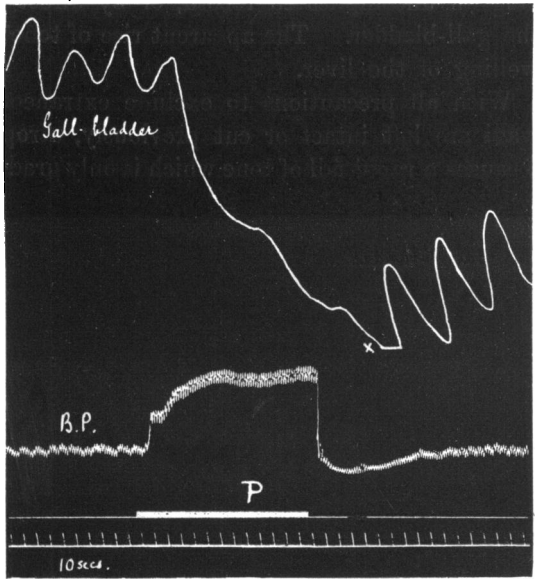


Fig. 17. $\times \frac{1}{2}$. Curare. Gall-bladder separated from liver. Chest opened and loop put round thoracic aorta. Blood-pressure from carotid. At *P* thoracic aorta occluded. At *X* lever of recorder reached its lower limit.

that of stimulating the sympathetic nerve-supply[1]. But here, as elsewhere, the inhibitory effect of sympathetic stimulation is shown to be independent of the associated local anæmia by the fact that it is easily obtained when vaso-constriction has been excluded by the action of chrysotoxin.

[1] Cf. Elliott. This *Journal*, xxxi. p. 164. 1904.

V. THE ACTION OF CERTAIN DRUGS.

Nicotine. The effect of intravenous injection of 2—4 mgms. of nicotine is indistinguishable from that of adrenalin, the stimulant effect on sympathetic ganglion cells entirely overpowering the concomitant excitation of ganglion cells on the course of the vagus fibres which must be supposed to take place.

Bile-salt. The muscle of the gall-bladder is affected like all other plain muscle by intravenous injection of bile-salt, its activity being depressed, and relaxation being the result.

Pilocarpine. When the gall-bladder is left in its natural relation to the liver pilocarpine causes an apparent increase of tone when injected intravenously. We have not been able to produce this effect under conditions giving an uncomplicated record, or by direct application of the drug to the gall-bladder. The apparent rise of tone was therefore due to the swelling of the liver.

Atropine. With all precautions to exclude extraneous effect, and whether the vagi are left intact or cut previously, atropine (5 mgms. intravenously) causes a rapid fall of tone which is only gradually regained

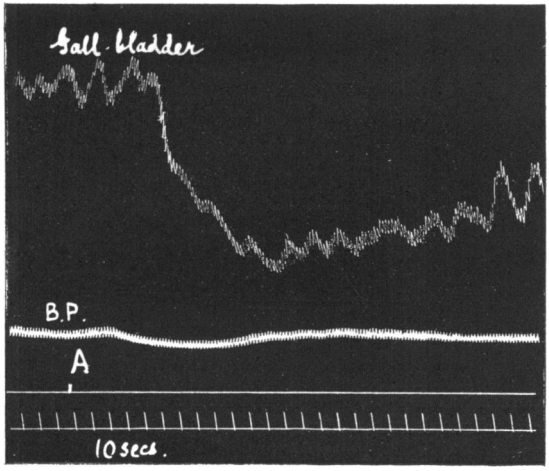


Fig. 18. × ⅓. Curare. Gall-bladder separated from liver. Blood-pressure from carotid. At *A* 5 mgm. atropine sulphate intravenously.

(Fig. 18). When atropine has thus been given, stimulation of either vagus produces no effect even when chrysotoxin has been given as well. The endings of the vagus in the gall-bladder would appear, therefore, to be more sensitive to atropine than those in the small intestine.

Amyl nitrite causes relaxation of the gall-bladder as of other plain muscular structures.

Peptone. Ellinger[1] states that intravenous injection of peptone causes contraction of the gall-bladder. We have found that the apparent contraction does, indeed, occur when the gall-bladder and liver are left in their natural relations. When arrangements are made to eliminate the effect of swelling of the liver the apparent contraction completely disappears, so that there can be no doubt that the increase of liver volume caused by injection of peptone entirely accounts for the phenomenon.

VI. THE QUESTION OF REFLEX ACTION THROUGH THE CENTRAL NERVOUS SYSTEM.

Heidenhain[2] attributed the first gush of bile, which he observed at a certain interval after a meal, to the passage of acid chyme over the biliary papilla causing a reflex stimulation of the gall-bladder.

Bruno[3], with a Pawlow fistula, did not observe this preliminary gush: but it is evident that his experiment does not invalidate the conclusion of Heidenhain, since the method of operation excludes contact of chyme with the papilla.

The discovery of secretin and its effect on secretion of bile suggested another possible explanation of the effect described by Heidenhain. The first effect of a rapid secretion of bile might cause a distension of the gall-bladder, which, upon the analogy of the intestine, might react by a sudden contraction. We have attempted to produce such an effect by sudden distension of the balloon in the gall-bladder with water. We observed no trace whatever of such a contractile reaction.

On the other hand we do not find, under the conditions of our experiments, any reflex effect on the gall-bladder contractions when acid (0·4% HCl) is injected into the duodenum or applied directly to the papilla, or when the papilla is electrically stimulated. It is impossible, however, to attach much significance to the failure to elicit such a reflex in an anæsthetised animal. Further, it is not improbable that a reaction to distension exists, which, like that of the urinary bladder, is dependent on a reflex through the central nervous system and abolished by anæsthetics. Our experiments, therefore, do not give any definite information

[1] Ellinger. *Hofmeister's Beiträg. z. chem. Phys. u. Path.* 1902.

[2] Heidenhain. *loc. cit.*

[3] Bruno. *St. Petersburg Arch. des Soc. Biol.* p. 87. 1899.

as to the method whereby the entry of gastric contents into the duodenum causes contraction of the gall-bladder—if it do so indeed. To settle this question would probably necessitate experiments on an animal with a permanent fistula of the gall-bladder.

SUMMARY AND CONCLUSIONS.

1. The gall-bladder shows rhythmic variation in volume: the rhythm is increased in extent after the removal of tonic inhibitory impulses either by section of the splanchnic nerves, or the intravenous injection of chrysotoxin. Spontaneous contractions of the gall-bladder had been previously observed by Doyon.

2. The normal effect of stimulation of the sympathetic nerve-supply to the muscular coat of the gall-bladder, whether by electrical excitation of the right splanchnic nerve or by intravenous injection of adrenalin, is relaxation.

The apparently motor effects first described by Doyon are in all probability due to extraneous causes, namely, the mechanical pressure on the gall-bladder caused by swelling of the liver, and the increased tone of the muscle due to hyperæmia.

We find, however, that the right splanchnic contains an admixture of motor fibres, the presence of which can be detected when the tone of the gall-bladder is lowered by enfeeblement or stoppage of the circulation.

3. We have confirmed the observations of Courtade and Guyon that the vagus contains motor fibres for the gall-bladder. Definite motor effects are obtained most readily by stimulating the vagus in the thorax after the administration of chrysotoxin. Both the tone and the rhythm of the muscular coat are augmented, though not necessarily to the same degree. The left vagus is the more effective of the two. The effect is abolished by atropine. Stimulation of the central end of the vagi has no influence on the gall-bladder.

4. We found it impossible under the conditions of our experiments to elicit a reflex contraction of the gall-bladder either by applying acid or the products of gastric digestion to the duodenal mucous membrane or the biliary papilla, or by electrical excitation of the papilla, or by rapid distension of the gall-bladder. We draw no conclusion, however, with regard to the existence of such reflexes in the unanæsthetised animal.

5. Bile-salt and amyl nitrite injected intravenously cause relaxation of the muscular wall of the gall-bladder; a similar effect is produced by atropine.

Pilocarpine and peptone cause an apparent contraction of the gall-bladder, but this is solely due to the mechanical effect of swelling of the liver. Neither of these drugs appears to have any effect on the gall-bladder itself.

6. Anæmia, caused by compression of the thoracic aorta, produces a rapid fall in the tone of the muscle of the gall-bladder.