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Ch.M. Thesis.

AN EXPERIMENTAL INVESTIGATION OF THE EFFECTS OF TRAUMA TO THE CENTRAL NERVOUS SYSTEM

by

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PART I.

1. INTRODUCTION.

This investigation was undertaken with a view of determining the nature of the "Shock", which is associated with trauma to the Central Nervous System. It deals with the effect of trauma to the Central Nervous System as opposed to the effects of trauma on the Central Nervous System, and the experiments performed have been confined mainly to the brain. It has been stated by some observers, that the condition known as shock cannot be produced by trauma to the Central Nervous System. Mann (1914) states, that it is impossible, even after hours of traumatisation to the great nerve trunks to produce shock in a dog, and that the only reliable method of doing so is to expose the intestines. Vincent (1918) states, that he has never seen injury either to the Central or Peripheral Nervous System produce shock. Porter, Marks and Swift (1907-8) showed, that stimulation of the central ends of the divided sciatic nerve, brachial nerves, posterior spinal roots, lumbar branches of the spinal nerves produced negative results. These stimulations failed to give a significant fall in blood pressure.

On the other hand, Guthrie (1917) claims to have

produced shock by stimulation of the sciatic nerves and brachial plexus; and Wiggers (1918) has produced what he called "Central Nervous System Shock" by prolonged stimulation of the sensory nerves.

In this investigation I have attempted to find out whether the shock to the Central Nervous System is of nervous origin, or if there be a chemical factor present, or if it be a combination of both factors.

It is well known, that operations on the Central Nervous System are accompanied by a fall of blood pressure, which may be marked, but that usually the blood pressure will recover if the operation be stopped; and a patient after a severe head injury is in a shocked condition.

I have divided this investigation into two main parts, the first dealing with trauma produced under various experimental conditions and also with the effects of intracranial pressure, and the second dealing with the question of the presence in the brain of a chemical substance or substances, which may cause a fall of blood pressure and produce shock.

2. METHODS.

In these experiments a large number of cats were used. The animals were in the first place anaesthetised in a box by means of chloroform to prevent the struggling and exhaustion, that follows the induction of anaesthesia in the cat with ether. The cats were then removed from the box, and tracheotomy was performed and a cannula was inserted into the trachea, after which intra-tracheal ether was administered for the duration of the experiment. In most cases a dissection was made to expose the carotid arteries, the jugular veins and the vagi nerves. In each case a blood pressure tracing was taken either from the carotid or femoral artery. In the experiments involving alteration of the intracranial pressure the blood pressure was taken from the carotid artery, but in those involving trauma to the skull and brain, the femoral artery was used in order to have the apparatus clear of the field of operation.

The T shaped glass cannula, which was inserted into the artery, was specially constructed with a view to minimising the risk of clotting of the blood. The cannula was attached by rubber tubing with a bottle containing a half saturated solution of sodium sulphate,

and with one limb of the mercury manometer.

In most of the experiments a tracing of the respira-: tory movements was taken. As a general rule it is difficult to obtain a satisfactory record of the respira-: tory movements, but for the purpose of my experiments, a specially designed stethograph was constructed for me by J.R.Bell and A.R.Smellie, who have described this instru-: ment in detail in "The Journal of Scientific Instruments, November 1933". This instrument is illustrated in Fig.1, which shows the main points of the instrument. It is a modification of the stethograph described by Sherrington.

A is a needle point which secures localisation on a circumscribed area of the chest. The sleeve B allows of minor adjustments. The counterpoise C to the chest arm is adjusted at the time of the experiment to the chest of the animal. The chest arm is connected to the short arm E of the recording lever by means of a rigid rod D, and the length of the rod may be altered. The recording lever itself may be lengthened or shortened by means of a friction - tight sleeve fitting F, and the frontal swivel writing point makes possible records of large amplitude. Coarse preliminary adjustments of the in-: strument to the animal and to the surface on which the

record is to be obtained is carried out by the slot G in the frame of the instrument, and by the boss head H, which fixes the entire apparatus to an upright rod. A hedgehog bristle is a very satisfactory point for writing on smoked paper.

In my hands, this instrument gave very satisfactory records of the respiratory movements.

Other operative procedures were performed, in addi-:tion to causing trauma and recording the intracranial pressure, such as removal of both stellate ganglia, division of the hypothalamus through the basi-sphenoid, etc. The technique of these experiments is described later.

In addition, numerous experiments for testing for the presence of depressor substances in the brain were carried out on the virgin uterus of the guinea pig, and on the small intestine of the cat. The duration of each experiment lasted up to 4 hours. In this thesis I have recorded only a limited number of the experiments and tracings actually made, but the results are based on the observations made during the entire series of the experiments.

3. DEFINITION OF SHOCK.

It is very difficult to give a satisfactory definition of shock. It may be defined as a condition of depression of the vital centres, associated with a profound disturbance of the circulation, causing a low pressure, and with a subnormal temperature and rapid shallow breathing. Meltzer (1908) emphasizes the fact, that it is only possible to give a clinical definition of shock; he defines it as "a state of general apathy, reduced sensibility, extreme motor weakness, great pallor, very rapid small pulse, thready soft arteries, irregular gasping respirations and subnormal temperature".

McDowall (1933) defines shock as "the state which results from a fall of arterial blood pressure, which if severe, may lead to death from oxygen want". The four vital processes are depressed, the temperature is subnormal, the respirations are shallow, the blood pressure is very low and the pulse is feeble and irregular, but in spite of this the patient is conscious.

4. THE NATURE OF SHOCK.

The term shock is often used very loosely, some refer to it as haemorrhagic shock, toxaemic shock, psychic shock, etc., but it is now customary to classify it as primary and

secondary; though Moulinier (1918) has classified shock according to its origin as nervous, haemorrhagic and infectious, and there is no doubt that each of these factors does play a part in the production of the condi-:tion. Before discussing further the nature of shock, I shall give a brief historical review of the subject and mention some of the older views.

Many theories of the cause of shock have been pro-:pounded from time to time, but many of them have been unsatisfactory, and it is questionable if any one of them really defines the nature of the condition.

Travers (1826) stated that "shock is a species of functional concussion by which the influence of the brain over the organ of circulation is deranged or suspended".

Reference to shock is also made in "The Medical and Surgical History of the War against Russia in the years 1854-55-56". In it, it is stated that "the shock of accidents frequently witnessed by the military surgeon differs often in a very material degree, and possibly in kind also, from that witnessed in civil life. When a cannon ball strikes a limb and carries it away ..... in the great majority of cases, the whole frame is likewise violently shaken and contused, and probably independent

of these physical injuries, a further vital influence is exerted which exists in a very minor degree, if at all, in the last named injuries, and may possibly de-:pend upon the ganglionic system".

Savory (1860) thought, that death from shock re-:sulted from sudden and violent impressions in some parts of the nervous system acting upon the heart. John Hunter, quoted by Morris (1867) is stated to have seen a man die almost immediately on the loss of a testicle. This type of shock is designated traumatic shock.

Probably what was really the first well defined theory of shock was that brought forward by Fischer (1890) who founded it on the well known experiment of Goltz. Fischer assumed that traumatic shock consisted of a vaso-motor paralysis, especially of the splanchnic area, with consequent anaemia of other parts. Shock was, in fact, a haemorrhage into the body's own large veins. Groeningen, quoted by Warren (1895) assumed that all nerve centres were equally affected, not by paralysis, but by exhaustion brought on by the traumatic over stimulation.

Kinneman (1903) put forward the hypothesis, that

shock was due to a derangement of the thermogenic centre. Vale (1904) suggested, that it is a condition of perverted metabolism due to trophic impulses. Bainbridge and Parkinson (1907) thought that it is due to pathological changes in the chromaffin tissue.

A good deal of discussion has been caused by the "Acapnia Theory" of Henderson (1908-9-10). He believes that shock may be caused by a loss of carbon dioxide by the tissues; the loss being brought about by excessive pulmonary ventilation by exhalation of carbon dioxide from the exposed viscera. He denies that vaso-motor failure is present in shock and claims that the development of shock may be prevented by safeguarding the body from loss of carbon dioxide. The opinion of Leonard Hill (1910) is that shock is due to a depression of the sensory synapses, producing a decrease of tone in the Central Nervous System. Other theories are, that shock is due to acidosis, suprarenal hyperactivity and hypoactivity, and fat embolism.

Primary "Shock", which is often referred to as "Collapse", has a nervous origin, and this was explained by Goltz (1863) who found that a blow on the exposed mesentery of a suspended frog caused a reflex inhibition of the heart, through the vagus, associated with a reflex dilatation of the arteries in

the splanchnic area, and Crile (1899) lent his support to the theory of vaso-motor exhaustion, and he thought, that the large amount of blood which accumulated in the veins was due to the low blood pressure asociated with exhaustion of the vaso-motor centre, and the accumulation of blood in large veins caused diminution of the diastolic filling and output of the heart. Later Crile (1914) was of the opinion that shock consisted of exhaustion of the cells in the brain, liver and suprarenals. The changes in shock and exhaustion from any cause seem to be identi-:cal. Crile concluded that the primary change wrought by all causes of shock is fatigue of the vaso-motor centre, and, as a consequence, there is a continuous lowering of the blood pressure until the cerebral centres no longer receive sufficient blood to enable them to function normally. Crile's view was supported by Mummery (1905). Boise (1907) and Malcolm (1905-07) are willing to accept the facts as reported by Crile, but attempt to interpret them differently. They believe, that the low blood pressure and venous stasis observed in surgical shock need not be due to paralysis of the blood vessels and exhaustion of the vaso-motor centre, but on the contrary can be the outcome of a high stimulation of the centre and

a strong contraction of the arteries. This view is not supported.

The view of Goltz seemed to support the idea that vaso-motor failure is the cause of shock. This view is vigorously opposed by Porter (1907) who showed that the effects of afferent impulses upon the vaso-motor centre are as great as when the blood pressure is 35 mm. Hg., as when the blood pressure preceding stimu-:lation is at the normal level, and that knowledge regarding the vaso-motor cells strengthens the belief that this endurance under stimulation is very great, but, on the other hand, they are extraordinary sensitive to variations in their blood supply. In another paper Porter and Quimby (1907) showed, that excessive stimula-:tion of the Depressor Nerve, which is the afferent nerve to the bulbar vaso-motor centre, did neither depress nor inhibit the cells of the vaso-motor centres, as would be expected if Crile's view were accepted, though, of course, it caused a fall of blood pressure.

The divergence of the views of Crile and Porter may be summarised as follows; according to Crile the failure of the blood pressure is the primary and sole cause of all symptoms of shock, and this failure has its cause solely the exhaustion of the vaso-motor centre. The

cardiac and respiratory failures and their phenomena are only secondary consequences or subsidiary factors to the primary cause i.e. the exhaustion of the vaso-motor centre.

Porter's views are entirely antagonistic to those of Crile. He states that, in numerous experiments he failed to find an instance in which the stimulation of the afferent nerve, except of course the depressor nerve, caused a sufficient fall of blood pressure. Crushing or electrical stimulation of the testis always caused a rise of blood pressure. Continuous stimulation of the central ends of the sciatic, brachial or other afferent nerves for many hours gave uniformly the same rise of pressure as at the beginning. Even in the experiments in which all the clinical signs of shock were present, stimulation of the depressor nerve lowered the blood pressure by 45%. He is emphatic, that the vaso-motor cells in shock are neither exhausted, depressed nor inhibited.

Janeway and Ewing (1914) think, if trauma to the sensory nerves is a factor in the production of shock, that it is only subsidiary to other factors. In their opinion the important factor is loss of vaso-motor control, or, at least, the impossibility of regaining this control, after it has reached a certain degree which determines the failure to recover. They think, that the loss of control

is never caused by acapnia or central nervous exhaustion. Apart from afferent impulses more especially splanchnic sensory impulses, which may have initiated the shock and contributed to it, the loss of control was, in their opinion, always due to local peripheral causes, which in their experiments were mechanical obstruction, loss of blood and trauma to the viscera.

In spite of complicating views regarding shock, it is generally accepted, that primary shock is probably due to afferent impulses, which cause a reflex dilatation and a profound fall of blood pressure, and that the diminished supply of blood to the brain may result in a loss of con-: sciousness. After a period either recovery takes place or the condition merges into delayed or secondary shock, which follows in a few hours. Secondary shock is now generally believed to be due to traumatic toxaemia. This affords the most satisfactory explanation, because secondary shock does not come on immediately, but its action is de-: layed, and it is often associated with damage to the muscles or multiple wounds. If absorption from the injured area be prevented, e.g. by clamping the veins of a crushed limb, the appearance of shock is delayed, and, if the clamp be removed, the characteristic symptoms reappear. In this

condition the blood vessels are narrowed, and the vaso-motor centre is not exhausted but still active. There are good reasons for believing, that the substance, which causes the secondary shock is histamine. This substance is present in the tissues, and is liberated by the most trivial injuries, and histamine poisoning resembles clearly many of the symptoms of shock. I shall deal in some detail with histamine at a later stage in this thesis.

In opposition to Crile's view, it may be pointed out that the vaso-constrictor centre is practically normal in shock, and Pike, Stewart and Guthrie (1908) have shown that the vaso-motor centre can withstand complete anaemia without losing its tone or reflex activity, better than any of the other cardinal centres. It is now known, that the arterioles are not dilated but contracted, and consequently the low blood pressure must be dependent upon an inadequate output of blood from the heart. This diminished output of the heart is largely due to the fact, that the arteries and veins are also contracted. It is well known how difficult it may be to insert a cannula into a superficial vein in a patient suffering from shock.

The constriction of the vessels is one cause of the

improper diastolic filling of the heart, but there is also another and important factor. If the heart does not fill properly during diastole, and at the same time the functions of the heart are unimpaired as they are in shock, it is obvious that this is due to an oligaemia. In cases of shock due to haemorrhage the cause of oligaemia is obvious. Where, however, there has been little or no haemorrhage, the cause of oligaemia is mainly the stagnation of the blood in the splanchnic area, in other words, the patient bleeds into his own vessels i.e. the capillaries and venules. Apart from the fact that much fluid is lost in the capillaries of the tissues outside the abdomen, it has been shown that a concentration of blood occurs in the capillaries, as indicated by comparisons of the corpuscles and haemoglobin in the blood drawn from capillaries and veins respectively. Krogh (1920-21) has demonstrated, that normally at any one time only a fraction of the capillary bed is in use, so that at any one time a large amount of blood could be re-:moved from the active circulation, by dilatation of additional capillaries, without any actual external loss. Robertson and Bock (1919) have pointed out, that the blood pressure in a given case is inversely proportional to this disparity in concentration between capillary and venous

blood; as the severity of the shock syndrome diminishes, this difference disappears, and the circulating blood volume increases.

5. CEREBROSPINAL FLUID.

The Cerebrospinal Fluid, which has been termed by Cushing the third circulation, has normally in man a pressure varying from 60 to 120 mm. of water. It fills the subarachnoid space, and forms a pad, which entirely encloses the brain and spinal cord, and the fluid surrounding the cord is in free communication with that in the brain. The amount of cerebrospinal fluid in man is said to be about 70 c.c., and if this be correct, it cannot form a thick pad round the nervous system. According to Stillman (1911) the amount normally increases with age, after puberty, as the brain shrinks in size. It can be formed quickly from the blood, and when in excess, be absorbed by the blood. Experimental work by Dandy and Blackfan (1913-17) indicates, that the cerebrospinal fluid is formed within the ventricles from the choroid plexuses, and probably its formation is due to active secretion of the epithelial cells covering these plexuses, but it may be due to mechanical filtration.

Becht (1920), however, says that there is no proof

that the cerebrospinal fluid is formed by secretion. The cerebrospinal fluid, which is formed within the ventricles, passes out through the Foramen of Magendie and the Foramina of Luschka into the Cisterna Magna and then passes either down the spinal subarachnoid space or forward over the base of the brain and cerebral hemispheres. Frazier and Peet (1915), and Weed and Cushing (1915) point out that the rapidity of the formation of the cerebrospinal fluid is increased apparently by pituitary extracts and diminished by thyroid extracts. The cerebrospinal fluid acts as a special buffer, and it probably regulates the contents of the cranium, draining away if the brain or blood volume increases, or more is retained if the brain shrinks. It probably acts as a medium for removing the products of metabolism of the central nervous system. It also has a protective reaction. It is always enclosed in dura mater and if it comes in contact with other tissues a new dura mater is rapidly formed.

Weed and McKibben (1919) have investigated the pressure of changes in the cerebrospinal fluid following intravenous injection of solutions of various concentrations. They found that the pressure of cerebrospinal fluid in etherised cats was about 119 mm. of this fluid, if read immediately after the connection of manometer

with needle in the subarachnoid space; if read some minutes later it rose to an average of 129 mm. due partly to re-: placement of the cerebrospinal fluid displaced in the manometer. The intravenous injection of Ringer's solu-: tion caused no lasting change in the pressure of the cerebrospinal fluid. Intravenous injection of hypotonic solutions, such as, distilled water, were followed by a marked and sustained rise in pressure of cerebrospinal fluid. Intravenous injection of hypertonic solutions, such as, sodium chloride and sodium bicarbonate, caused an initial rise in the pressure of the cerebrospinal fluid which was followed immediately by a marked fall in this pressure often to zero. In a later paper Weed and Hughson (1921) found that the cerebrospinal fluid pressure is invariably higher than that of the brachial veins, ex-: cept after the intravenous injection of strongly hypertonic solutions.

Changes in the cerebrospinal fluid pressure induced by the intravenous injection of solutions of various concentra-: tions seem to be independent of the changes in the systemic arteries or venous pressure. According to Becht (1920) the venous and cerebrospinal fluid pressure while positive in normal animals are always less than the arterial pressure, and the venous and cerebrospinal fluid are almost but not

exactly equal. The venous and fluid pressure vary in the same direction, and are to some degree proportional in nearly every case. These pressures may or may not vary in the same direction as arterial pressure. Raising the venous pressure raises the fluid pressure and vice versa. Increasing or decreasing the fluid pressure moderately does not alter the venous pressure, unless the arterial pressure is affected, and the arterial pressure can modify the cerebrospinal fluid pressure independently of the venous pressure. The fluid pressure is the result of at least two factors, the influence of the venous pressure and the influence of the arterial pressure.

The cerebrospinal fluid pressure is influenced passive-:ly to a small extent by changes in the arterial and venous pressure, and such alterations are insignificant compared with the independent changes in pressure, which occur as a result of secretory activity. Dixon and Halliburton (1914) think that of all the conditions which influence the cerebrospinal secretion the most important are deficiency of oxygen or excess of carbon dioxide in the blood.

Ritchie Russell (1931) observed a number of cases of head injuries, and in a number of these he investigated the cerebrospinal fluid. It is interesting to note that in

twelve cases, where the mental state was normal, the pressure was over 200 mm. of water, and in none of the cases which were comatose did the pressure rise above 200 mm. This, according to him, would lead to the conclusion, that high intracranial pressure is not an essential factor in producing the gravity of head injuries.

6. INTRACRANIAL PRESSURE.

Intracranial pressure is the pressure in the space between the skull and the brain, and therefore the pressure in the subarachnoid space, and also the pressure in the ventricles, since they are in communication. This pressure is the same as the venous pressure within the sinusus. The large veins are surrounded by the cerebrospinal fluid, and consequently an equilibrium of pressure may be established between them. A rise of intracranial pressure raises the venous pressure by compression of the veins, and by acceleration of the flow of fluid from the subarachnoid space into the venous circulation. Presumably an increase of venous pressure will cause a corresponding rise in the intracranial pressure due to compression following the expansions of the venous wall, and to the retardation of the inflow of the cerebrospinal fluid into the veins.

Three grades of pressure can be distinguished as prevailing within the skull. Firstly, the general intracranial

tension, which is that of the veins, sinusus and cere-
:brospinal fluid of the ventricles, and cisternae. This
is a low pressure, and is subject to respiratory fluctua-
:tions. Secondly, the capillary pressure, which is that
of the brain substance itself, that is, it represents
most of the resistance, which the brain offers, when pres-
:sure is made upon it.

In compressing a part of the brain until it is rendered anaemic the capillary pressure has to be overcome in addition to the slight elasticity of the brain substance. Thirdly, the arterial pressure. The arteries supplying the brain contain blood under a pressure the same as that in the carotid arteries, but this high pressure is shut off from being communicated to the brain substance or the cerebro-
:spinal fluid. The effect of a rise of the carotid pressure is to accelerate the rate of the flow of blood through the brain. It can have no other effect so long as the arteries do not give way, and can, therefore, in itself produce no effect on function.

Since the brain and its vessels and lymphatics are en-
:closed in a boney case, it has generally been assumed, that the brain and its vessels occupy the whole skull, and, that the brain being incompressable, the total blood content is almost constant. This hypothesis is generally spoken of

as the Monro-Kellie doctrine, and it has obtained general consent.

The cranial cavity being relatively fixed in volume, and being completely filled with the brain, cerebrospinal fluid and blood, variations in any one of these three ele-:ments may occur, and compensation is afforded by alteration in the volume of one or both of the remaining elements. Weed and Hughson (1921) are of the opinion that the boney coverings of the central nervous system constitute, within tested physiological limits, inelastic and rigid containers, and the ordinary laws of a "closed box" may therefore be applied to the cranium. The advocates of this view sug-:gest, that as the brain can increase its blood contents only by turning out the cerebrospinal fluid, when this fluid has gone the brain comes in contact with the skull, so that no further expansion of the vessels can occur.

Becht (1920) also pointed out, that both the brain and spinal cord because of their large water content are prac-:tically incompressable, and because of its boney structure the skull and neural canal are nearly undilatable to pressure except at the membranes covering the foramina between the vertebrae. To the same degree that the brain is incom-:pressable and the skull undilatable pressure, they are lacking in elastic recoil, when the pressure is removed.

It has been emphasized by some observers, that the first effect of any encroachment on the intracranial space is to drive out the small amount of cerebrospinal fluid normally present, but Cushing has pointed out, that this is not invariable since compression associated with increase of fluid is often seen as in acute traumatic ocdema or the so called "traumatic serous meningitis". Compression does not, therefore, necessarily mean a dry brain, for interference with the foramina of outflow may result in the swelling of the brain. A further encroachment can occur only by crowding out the contents of the blood vessels, and as the tension of the cerebral veins is lowered, these vessels are affected first, and as a result venous stasis is one of the first effects. A still further pressure brings the pressure exerted on the brain up to the pressure in the capillaries or in the arteries, and thereby causes anaemia of the brain.

Although it has been stated by many observers that the brain is incompressable, its volume can be altered under experimental conditions. Weed and McKibben (1919) found, that intravenous injection of hypertonic solutions, such as 30% of sodium chloride or saturated solutions of sodium bicarbonate, is followed by a marked decrease in the size of the brain. After this treatment, if the skull be opened,

the brain may be seen to fall away several millimetres from the inner surface of the skull. On the other hand, the intravenous injection of hypotonic solutions, such as water, causes a marked swelling of the brain and when openings are made in the skull the brain rises and forms herniae through the trephine openings. These changes are independent of the volume of fluid injected and are probably due to the fundamental osmotic effects of the hypertonic and hypotonic solutions. In the opinion of Weed and McKibben, the brain should no longer be considered as incompressable and of fixed volume as the earlier writers assumed, but as subject to variation in size under experimental conditions. Dixon and Halliburton (1914) are also of the opinion, that the brain cannot any longer be regarded as a fixed quantity without the power of expanding or contracting in volume.

Intracranial pressure may be local or general, in the case of general pressure, the cranio-vertebral canal forms one continuous system. Nnaunyn and Schreiber (1882) distinguished two methods of studying general compression, in one the compressing fluid was allowed to enter the space between the skull and dura, i.e. "extra-pial compression" and in the other to enter the subarachnoid space i.e. "intra-pial compression". They observed no difference in the results of these two methods.

Hill (1896) has shown that the brain does not transmit local pressure equally in all directions. The effects depend to a large degree upon the proximity of such compression to the medullary centres, or upon the position of the compression in so far as it may indirectly cause compression of these centres e.g. by forcing the medullary into the Foramen Magnum. The pressure discontinuity is effected by the viscosity of the brain substance, by the Tentorium Cerebelli, by the Falciformm Ligament and by the plugging of the Isthmus Tentorii Cerebelli and Foramen Magnum by the dislocation of the brain mass.

Normally the intracranial pressure is the same in differ-: ent parts of the skull, but in abnormal conditions, owing to the dislocation of the brain the septa of the dura may act as effectual partitions, and in these circumstances different pressures may prevail in different parts of the skull. Because there is a considerable pressure discontinuity between the three intracranial compartments, the pressure effects of a local process are greater in its immediate neighbourhood than at a distance. A local process over one cerebral hemisphere may exceed the local arterial pressure, and produce a local anaemia which is sufficient to throw the adjoining parts of the brain out of function without seriously affecting the other hemisphere or the subtentorial structures. On the other hand, if a compression of similar degree were distributed

equally throughout the cranial chamber by means of fluid let into the subdural space, a generalised anaemia would follow, and death from implication of the vital centre in the medulla would be the result.

Astley Cooper (1824) trephined the skull of a dog, and pressed with his finger on the dura mater, the dog became insensible then comatose, and the pulse slow. When the pressure was relaxed the animal completely re-:covered consciousness. Francois Franck (1877) observed the effects of compression on the brain in dogs, and par-:ticularly noted the respiratory paralysis and elevation of the arterial pressure. Nnaunyn and Schreiber (1883) stated, that the effects of cerebral compression are most marked when the compression exceeds the normal arterial pressure. They drew attention to the rise of arterial pressure and to the occurrence of Traube Hering Waves.

Spencer and Horsley (1891), and later Horsley and Kramer (1897) working on dogs produced compression of the brain by inserting a bag into the cranial cavity through a trephine opening. They used thin walled easily dis-:tended bags both pear shaped and globular. Each bag was continuous at its neck with a stiff metal tube, the other end of which was connected with the lower end of a burette, which was filled with mercury. When the

burette was raised above the level of the bag, the latter became distended with mercury. They found that the primary cause of death was due to the arrest of respira-:tion, and not to failure of the circulation. Cushing does not agree with Horsley on the primary importance of respiratory failure. He placed a rubber bag containing fluid through a trephine hole in the skull, the opening in the skull was occluded, and the bag was connected with a manometer, so that the pressure could be altered at will. This experiment was repeated by Eyster (1906).

Cushing (1902) and Eyster, Burrows and Essick (1909) observed that, so long as the intracranial pressure re-:mains below that of the arteries supplying the brain, the circulation through the brain is not markably affected, but, if the intracranial pressure rises above the general arterial blood pressure, the flow through the substance of the brain is prevented, and anaemia of the brain results. The explanation is that if the pressure in the bag, which is comparable to the finger pressure used in my first series of cats, and to the experimental method of increas-:ing the pressure in one of my later series of cats, is raised, it is propagated to all parts of the skull contents, and also to the subtentorial space where the vital centres are situated. The first effect of the increased pressure

in the subtentorial space is stasis in the capillaries of the medulla with stimulation of the respiratory centre. With a further increase of pressure, the medullary capill-:aries are emptied and as a result anaemia ensues, which stimulates the vaso-motor centre, and causes a rise of blood pressure. When the blood pressure has become higher than the cerebral pressure, the medulla is provided again with oxygenated blood, and when the carbon dioxide of the blood has reached subnormal values, apnoea ensues. This sequence may repeat itself, and is known as Cheyne Stokes breathing. Cushing calls them exaggerated Traube Hering Waves.

The origin of this type of respiration must be sought for in the oscillation of the blood pressure. The vaso-:constrictor centre is a tonically acting one, and it is capable of exhibiting rhythmicality, and this rhythmic activity is seen in the Traube Hering Waves. These waves are produced by the vaso-constrictor centre sending out stronger then weaker impulses. These Traube Hering Waves are common in cerebral compression.

In connection with the intracranial pressure, it is interesting to note its effect on the reflexes of the carotid sinus. Since the work of Hering (1927) the "depressor" action of the carotid sinus has been admitted,

but there is some doubt concerning its "pressor" action, which results from an increase of blood pressure in the sinus. There is a possibility that the carotid sinus played some part in Cushing's results, possibly by increasing the resistance to the carotid flow. The increased intracranial pressure might elicit the direct pressor reflex of the sinus.

Heymans (1928) studied the effect of intracranial pressure on the rate of the heart before and after denervation of the carotid sinus. A rise of intracranial pressure leads first to a slowing of the heart, then to a short acceleration which is followed in turn by a marked slowing. He raised the intracranial pressure before and after denervating the carotid sinus, and got the same effects. He concluded that the action of the intracranial pressure is entirely central, in contrast to the slowing of the heart due to increased cephalic blood pressure, an effect which originates in the carotid sinus.

Izquierdo (1930) studied the influence of the aortic and carotid sinus reflexes on the height and form of the rise of blood pressure produced by peripheral stimulation of the splanchnic nerves. If one assumes, as Cushing did, that the rise of blood pressure following intracranial

pressure is due to direct stimulation of the vaso-motor centre, then this rise is due mainly to the action of the splanchnic nerves. Izquierdo stimulated the splanchnic nerves peripherally with a faradic stimulus, and found that when he had extirpated all four depressor zones, i.e. the two carotid sinuses and the two aortic zones, the blood pressure rose very much higher than before. He showed, that if all four depressor zones were present, their joint inhibitory action was so great in some cases, that stimulation of the splanchnic nerves had little effect. He concluded that the mechanism of the increase in blood pressure on stimulation of the splanchnic nerves was the result of two factors, firstly, a factor of direct vaso-motor stimulation, and secondly, an indirect or secondary depressor factor due especially to the carotid sinuses.

Guernsey, Weisman and Scott (1933), while testing the intracranial pressure, stimulated the carotid sinus either electrically or mechanically and found that, even if the intracranial pressure was greater than the blood pressure, stimulation of the sinus always produced a fall of blood pressure, which was greater than that which would occur under normal conditions of intracranial pressure. In some experiments the intracranial pressure was raised after

denervation of the carotid sinus, and the result was a rise of blood pressure greater than before, and the blood pressure rose more promptly and to a greater height than before. In other experiments in addition to denervation of the sinuses, the two depressor nerves were cut, and the responses tended to be better than before denervation. These results led them to believe, that the carotid sinus is not primarily concerned with the mechanism described by Cushing, and that his conclu-: sions that the mechanism is a central one, probably effected by anaemia of the medullary centres, is probably correct.

7. EXPERIMENTAL WORK ON TRAUMA AND INTRACRANIAL PRESSURE.

Trauma to the central nervous system was studied ex-: perimentally by trephining the skull, and causing trauma directly to the brain either by pressure of the finger or by damaging the brain by instruments, and also by forcing fluid through the trephine openings. The last method produced a general increase of intracranial pressure.

The apparatus which I designed for recording the intracranial pressure is shown in Fig. 2. It consisted of an adjustable stand for the manometer (1), which con-

:tained a writing style (2) and a pressure bottle (3), which contained Tyrode Bayliss solution. A pressure bulb with a button release was connected to the top of the pressure bottle. Through an opening near the bottom of the pressure bottle a Y tube was inserted,one limb of which connected the pressure bottle with the manometer and the other with one end of the T shaped cannula (5). A screw clamp was attached to the other end of the brass cannula. The brass cannula had a threaded end which was screwed into the trephine opening.

The intracranial pressure was raised by pumping the pressure bulb and maintaining it at the particular level desired by screwing the button. The pressure communi-:cated to the brain was simultaneously communicated to the manometer and recorded on the revolving drum by the writing style. In order to communicate the pressure suddenly to the brain, a clamp was placed in the tube between the T shaped cannula and the pressure bottle. The pressure in the apparatus was then raised, and by removing the clamp this pressure was suddenly communi-:cated to the brain. On the other hand the intra-:cranial pressure could be gradually raised by pumping the pressure bulb and screwing the button release at any desired level, in this case no clamp was used between the

T shaped cannula and the pressure bottle.

In the first series of experiments pressure was applied through the trephine opening by means of the finger, and this caused a local pressure, resembling the pressure exerted by the rubber bag inserted through a trephine hole, which has been used by Cushing and other observers. The results of local pressure ap-:plied in this way with the dura mater intact are seen in Fig. 3. At A, pressure was applied through the trephine hole, and at B, the pressure was removed, and the blood pressure fell from 146 mm. Hg. to 46 mm. Hg, but it recovered without the aid of artificial respira-:tion shortly after the pressure had been removed. Fig. 4 is from the same experiment, pressure was again applied at A, and there was an immediate rise of blood pressure, followed by a marked fall; at B, the pressure was removed, and the blood pressure recovered. In Fig. 5, pressure was applied at A, and there was a small rise of blood pressure then a marked fall. When the pressure was removed at B, the animal had stopped breathing and artificial respiration had to be started. Fig. 6 was taken from a female cat weighing 2.4 K. At A, pressure was applied to the brain, this was followed

by a small rise of blood pressure, then by a marked fall and the animal collapsed and artificial respiration had to be started at B.

Fig. 7 was taken from a female cat weighing 3.1 K, the blood pressure was taken from the femoral artery. In this figure a tracing of the respiratory movements is also recorded. At A, pressure was applied to the intact dura mater; there was a small rise of blood pressure, followed as before by a fall. Very shortly after the pressure was applied, the respiration ceased and to pre-:vent the animal dying, artificial respiration was started at B. At C, the artificial respiration was stopped and the animal breathed itself, and the blood pressure rose higher than the original pressure.

Fig. 8 was from the same animal, at A, pressure was applied. The duration of the pressure is indicated by the signal, the same results as before followed in this case. At B, owing to the cessation of respiration, artificial respiration had to be started. At C, the artificial respiration was stopped, and this was followed by convulsions. After a short interval the blood pres-:sure rose and the respirations became normal. At D, the right vagus was divided and at E, the left vagus was divided, and the blood pressure rose and the respirations

became slower.

The same results were observed in many other similar experiments. From these tracings it is observed, that when local pressure is applied to the brain, either through the intact dura mater or directly on the brain, after a short interval there is a small but distinct rise of the blood pressure associated with cessation of respiration. Immediately following the preliminary rise the blood pressure falls sharply even after the pressure has been removed from the brain. In some cases the respiration and blood pressure gradually recover, when the pressure is removed, but usually artificial respiration is required to prevent the animal dying. When the blood pressure recovers, it sometimes but not always rises to a higher level than before.

The preliminary rise of blood pressure is probably due to the anaemia of the brain stimulating the vaso-motor centre in an attempt to overcome the anaemia, but if the pressure is sustained, the anaemia soon involves all the vital centres in the medulla, and the respiratory centre fails. In the experiments in which local pressure was applied, it made no difference whether the dura was intact or divided, and in all the animals used, I found that a very moderate degree of pressure applied locally

for a very short interval caused a marked fall of blood pressure, usually associated with failure of the respira-:tory centre. As a result of these experiments I am of opinion that local pressure applied over one cerebral hemisphere, unless very slight, may rapidly spread through-:out the brain and involve the medullary centres.

In Fig. 9, at A, a small portion of the brain was removed and pressure was applied to control the haemorrhage, the rise of blood pressure here is probably due to the pressure. At B, the pressure was removed, at C artifi-:cial respiration was started, and stopped at D. In Fig.10 at A, an instrument was introduced through a small trephine hole, and stirred round in the brain. In this case there was a long latent period before there was a marked fall of blood pressure. The fall here may be due to the libera-:tion of depressor substances, which are present in the brain, as I have demonstrated at a later stage of this thesis.

Kramer and Horsley (1897) experimented with dogs, which were shot with bullets of various calibre. As a result of extensive experiments they found that the prim-:ary oause of death consisted of sudden cessation of the respiration, which, however, could be artificially restored.

They found that a bullet passing through the cerebral hemi-: spheres immediately produces a severe elevation of intracranial pressure, which induces a state of compression of the brain. The second cause of death is haemorrhage, which consequently leads to a further elevation of the intracranial pressure.

The effect of raising the intracranial pressure is seen in Fig. 11. This was a male cat weighing 3.2 K. The blood pressure tracing was taken from the left femoral artery; the skull was trephined and a T shaped brass cannula was screwed into the trephine hole and connected by means of tubing with the recording apparatus. At A, the blood pres-: sure was 138 mm. Hg and the pressure in the apparatus was raised to 105 mm. Hg. At B, this pressure was suddenly communicated to the brain by removing the clamp. The re-: sults were a slight rise of blood pressure and cessation of respiration for a short period. The interval between B and C indicates the time which this intracranial pressure was applied to the brain. At C, the intracranial pressure was suddenly lowered to zero, and this caused no effect other than, that the respirations were not so rapid as they were before the intracranial pressure was raised. Similar results are shown at E, where the initial blood pressure

was 140 mm. Hg and the intracranial pressure was raised to 115 mm. Hg and at F, the blood pressure was 130 mm. Hg and the pressure in the apparatus was raised to 125 mm. Hg. At G, this pressure was suddenly communicated to the brain. There was as before a small preliminary rise of blood pressure, but after a short interval the blood pressure began to fall. At H, the intracranial pressure was suddenly lowered to zero. After removal of the intracranial pressure, the blood pressure continued to fall until it reached about 65 mm. Hg, and then it gradually recovered and the respirations became more rapid.

Fig. 12 was taken from another cat, which was prepared in the same way. At A, the blood pressure was 125 mm. Hg, and the pressure in the apparatus was raised to 135 mm. Hg, and at B, this pressure was suddenly communicated to the brain. This was followed by a rise of blood pressure accompanied by slowing of the respirations, and as the high intracranial pressure was maintained the respirations ceased. At C, the intracranial pressure was suddenly lowered to zero, and the blood pressure continued to fall until it was only 25 mm. Hg. This was followed by a gradual restoration of the blood pressure and the respirations recommenced slowly without the aid of artificial respiration.

Fig. 13 was taken from a male cat weighing 3.4 K. At A, the blood pressure was 120 mm. Hg, and the pressure in the apparatus was raised to 130 mm. Hg, and at B, this pressure was communicated to the brain. At C, the intracranial pressure was lowered to zero and the blood pressure fell to 25 mm. Hg. At D, artificial respiration was started, but the blood pressure did not recover and the cat died.

These tracings show that firstly, provided the intracranial pressure remains below the blood pressure neither the respirations nor the blood pressure is affected. Secondly, when the intracranial pressure approximates the blood pressure, the latter shows a small rise. Thirdly, if the intracranial pressure is above the blood pressure, not only is there a preliminary rise of the blood pressure, but the respirations become slower and finally cease, and the blood pressure starts to fall, and even when the intracranial pressure is suddenly lowered to zero, the blood pressure continues to fall rapidly and generally artificial respiration is necessary to prevent the animal dying. Fourthly, after the pressure has been removed, the respiratory centre and blood pressure usually recover, either spontaneously or with the aid of artificial respiration. In these experiments, which I have mentioned, the intracranial

pressure was suddenly raised. If it be raised to the level of or above the blood pressure, it may cause a obmplete checking of the heart, which may last for 30 seconds, due to marked stimulation of the vagi. If the intracranial pres-: sure be held at this level, there is a gradual release from this vagus inhibition, the heart rate slowly returns to its normal rate, and the blood pressure ascends to its necessary level.

Eyster (1906) has pointed out that after a rise of intracranial pressure, the vagus inhibition does not de-: velop as a rule until the intracranial pressure reaches the level of the arterial blood pressure, and that this vagus inhibition passes off to a great extent with the following rise of blood pressure above the intracranial pressure, though it nearly always persists to a certain degree. Cushing (1901) has laid down a law that "an increase of intracranial tension occasions a rise of blood pressure which tends to find a level slightly above that of the pressure exerted against the medulla". The small rise of blood pressure, which occurs immediately the intra-: cranial pressure exceeds the blood pressure, is probably due to stimulation of the vaso-motor centre, which is attempting to counteract the condition of bulbar anaemia. By employing a cerebral window placed in a trephine hole

Cushing noticed that, when the intracranial pressure was higher than the blood pressure, the capillaries of the cortex were blanched.

If the intracranial pressure, when it exceeds the blood pressure, be suddenly communicated to the brain there may be, as has been pointed out by Cushing and others, temporarily the so called major symptoms of compression with Kussmaul-Tenner spasms, i.e. evacuation of the bladder and rectum, cessation of respiration and pronounced vagus effect on the heart. This is followed by a release from this marked vagus inhibition, and the vaso-motor centre begins again to exerts its influence. These Kussmaul-Tenner anaemic spasms can only be produced when the anaemia is sudden in origin.

It has been seen from the tracings that if the intracranial pressure is higher than the blood pressure, and if the intracranial pressure is suddenly lowered to zero, the blood pressure falls rapidly. Normally the vagus exerts a continuous restraining action on the rate of the heart, and it diminishes the excitability, the strength of contraction and the conductivity from auricle to ventricle. If both vagi be divided the heart as a rule beats more frequently. The cardiac fibres of the vagus arise from the cardio-inhibitory centre, which is pre-

:sumably either part of or closely related to the dorsal nucleus of the vagus. Stimulation of the cardio-inhibitory centre, in intracranial pressure may be induced in three ways. Firstly, by anaemia; secondly, by a considerable and sudden increase of blood pressure in the medulla; and thirdly, as a result of asphyxia. The first of these is probably the one acting, when the intracranial pressure is raised. Eyster, Burrows and Essick (1909) have pointed out that the second cause of vagus inhibition, which is caused by a sudden lower-:ing of the intracranial pressure from a point above the blood pressure to a point considerably below it, is due to a sudden flow of blood to the brain, and a rapid increase of pressure there, which may produce a marked inhibition. They have shown that if the arterial pressure of the Circle of Willis be recorded simultaneously, a sudden sharp rise of this pressure is seen to occur, and this rise is co-incident with the inhibition.

Fig. 14, shows the effect of raising the intracranial pressure, when the vagi have been divided. This animal was a female cat weighing 2 K, both vagi were divided 25 minutes before the intracranial pressure was raised. At A, the pressure in the apparatus was raised to 130 mm. Hg, and at B, was communicated to the brain, and the blood pressure rose from 125 mm. Hg to 130 mm. Hg. At C, the intracranial

pressure was suddenly lowered to zero, and it is seen that there is no appreciable fall of blood pressure. This is presumably due to the fact that the vagi being divided the increase of blood pressure in the brain does not affect the cardio-inhibitory centre. The only effect on respira-:tion was a slowing.

The same effect is seen in Fig. 15. At A, the pressure in the apparatus was raised to 120 mm. Hg, and at B, it was communicated to the brain and the blood pressure rose from 115 mm. Hg to 120 mm. Hg, and when the intra-:cranial pressure at C was lowered suddenly to zero the blood pressure was 115 mm. Hg. Respiration was also slowed.

Injection of atropine has the same effect as division of both vagi, as is shown in Fig. 16. This was a female cat weighing 3 K. It was given an intravenous injection of 3 mg of atropine, but the vagi were left intact. At A, the pressure in the apparatus was raised to 110 mm. Hg, and at B, it was communicated to the brain. The blood pressure rose from 110 mm. Hg to 115 mm. Hg. At C, the intracranial pressure was suddenly lowered to zero, and the blood pressure was then 110 mm. Hg. The respirations became slower.

Fig. 17 shows the effect of gradually raising the intracranial pressure to a level greater than that of the blood pressure, and then lowering it to a level below that

of the blood pressure. It is seen as a result of this procedure, there is very little effect on the blood pressure, but the respirations are slowed but not stopped. Fig. 18 again shows the effect of gradually raising the intracranial pressure to a point higher than the blood pressure, and then suddenly lowering the intracranial pressure to zero. In this case the fall of blood pressure was not so marked as when the intracranial pressure was raised suddenly. Fig. 19 shows the effect of gradually raising and lowering the intracranial pressure. At A, artificial respiration was started and there was no fall of blood pressure in this case.

In Fig. 20 the intracranial pressure was gradually raised and was accompanied by a slight and gradual rise of blood pressure. At the highest point of the intracranial pressure respiration ceased, and the blood pressure fell as the intracranial pressure was lowered. At A, artificial respiration was started, and was stopped at B, and the blood pressure rose to a higher level than before. Much the same result is shown in Fig. 21, at A, artificial respiration was started. Fig. 22 shows the great extent to which the intracranial pressure can be raised, provided that artificial respiration is maintained; in this case both vagi were divided.

These experiments showed that when intracranial pressure is gradually raised from zero, there is as a rule no effect on respiration until the pressure of the compressing fluid rises almost to the mean of the blood pressure; then the respirations undergo a diminution in depth and rate leading to apnoea. This is usually followed by a development of the vagus inhibition associated with a fall of blood pressure, usually rendering artificial respiration necessary.

8. THE ACCESSORY SYMPATHETIC CENTRES IN THE HYPOTHALAMUS.

It was pointed out by Levy (1912) that the heart of the cat tends to develop ventricular extrasystoles, when the animal is under chloroform anaesthesia, and that these irregularities are often followed by fibrillation, and that the removal of the sympathetic nerves to the heart and removal of the suprarenals rendered the heart immune to these irregularities. Beattie, Brow and Long (1930) attempted to locate the area of the brain, removal of which was responsible for these phenomena. They succeeded in showing that a section of the brain from the anterior edge of the superior colliculus behind, to the level of the mammillary bodies ventrally, abolished the extrasystoles, and that these could not be made to reappear by the subse-

:quent application of chloroform. From their experiments they concluded that the centre involved lay at this area, and close to the middle line below the thalamic commissure. They were able to locate a definite region limited anterior-:ly and superiorly by a line joining the anterior edge of the superior colliculus to the posterior edge of the optic chiasma, and posteriorly a line joining the anterior edge of the superior colliculus to the posterior edge of the mammillary bodies. They found that within this area there is a centre or centres, the removal of which causes the abolition of the extrasystoles. They have shown that experimental lesions involving certain nuclei of the posterior part of the hypothalamus are followed by descend-:ing degeneration into the spinal cord, and that the fibre tracts pass partly to the Formatio Reticularis of the brain stem and partly into the intermedio-lateral columns of the grey matter in the thoracic and upper lumbar part of the spinal cord. They also brought forward evidence to de-:monstrate that the descending hypothalamo-spinal tracts play an important part in the control of the bulbar and spinal sympathetic nuclei. Karplus and Kreidl (1910) described a subthalamic centre in cats.

The work of Karplus and Kreidl, and of Beattie, Brow

and Long on the presence of hypothalamic centres associated with the sympathetic nervous system suggested, that this area might in some way be related to the effects of trauma to the brain. It was accordingly decided to divide the hypothalamus in the area described by Beattie, Brow and Long, and thereafter to apply trauma to the brain. In order to investigate this point the brain was exposed through the basi-sphenoid.

Other evidence in favour of the presence of centres in the hypothalamus associated with the sympathetic nervous system is provided by the work of Houssay and Mollinelli (1925) which showed that the stimulation of masses of grey matter on the ventral aspects of the third ventricle caused a marked secretion of adrenalin. Karplus and Kreidl (1927) showed that following stimulation of the hypothalamus there was a marked rise in blood pressure, and that when the splanchnics were divided the pressor effect was greatly diminished. Cannon and Rapport (1921) showed that there were two regions in the brain stem one in the hypothalamus and the other in the bulb, which when stimulated caused a rise of blood pressure and secretion of adrenalin. Recent work has indicated that there probably exists in the hypothalamus, nuclei which influence the reaction of the sympathetic nervous sytem. Fulton and Ingraham (1929) acting on the supposition that the frontal lobes give rise to tracts of fibres which pass to the

centres in the hypothalamus, attempted to sever this pathway and thus release the hypothalamus from the control exerted by the frontal lobes. To do this they made an incision anterior to the optic chiasma. They found that after this operation previously docile cats became vicious. They thought that the fact of dividing the cortico-hypothalamic tracts released the hypothalamus, and thus induced a state of chronic rage and that associated with this there was a diffuse discharge of the sympathetic nervous system.

The work of these observers indicates that there are centres in the hypothalamus which regulate the secretion of adrenalin and that the sympathetic centres of the hypothala-:mus do influence the heart rate. Bard (1928) advanced the view that the diencephalic representatives of the sympathetic nervous system consists of mechanisms, which are responsible for the activation of that system under conditions of stress.

9. EXPOSURE OF THE HYPOTHALAMUS

(a) Anatomy.

The area of the base of the skull of the cat, which is concerned in the exposure of the hypothalamus is the sphenoid. In the cat the sphenoid is irregularly five sided, the middle portion is the body, which is thick and narrow in front, but flatter, shallower and wider behind. The bone is divided into an anterior subtriangular part called the anterior

sphenoid, and a posterior quadrate part called the posterior sphenoid. The middle region of the anterior sphenoid is formed by the presphenoid. The lateral masses are the orbito-sphenoids or small wings, the portion of the body belonging to the posterior sphenoid is the basi-sphenoid and the lateral parts are the alisphenoids or great wings. The anterior sphenoid is composed of the median unpaired presphenoid and the lateral paired orbito-sphenoids. It is so covered below by the palatines and pterygoids, that only a narrow median strip of the presphenoid is visible on the under surface of the skull. The orbito-sphenoids are always firmly fixed to the presphenoid and cannot be clearly defined.

On the inferior surface of the presphenoid in the middle line is a smooth median ridge, the only part of the bone which shows on the outside or base of the skull. It is rounded and varies in width, but almost always presents a middle flatter and wider part. The posterior surface of the anterior sphenoid is small, circular and rough for the attachment to the basi-sphenoid.

The posterior sphenoid consists of two thin crescentic lateral plates, the alisphenoids, which are united at the back part of their inner edges by a central, flattened transverse piece which is the basi-sphenoid. From each

alisphenoid at its position of union with the basi-sphenoid in front, a plate-like horizontal process projects down-:wards and forwards, this is the pterygoid process. The inferior surface of the basi-sphenoid consists of a central flattened area, which is quadrate. The anterior angles are cut off by the rounded inner posterior angles of the pterygoid processes leaving a short straight transverse anterior border between them which is called the inter-:sphenoid suture, and just behind this is the vascular spot which is always present and which, in my experience, formed a very good landmark.

The under surface of the pterygoid process is sharply defined behind. The outer border is thin and about half of its length is prolonged into a variable external pterygoid process, which points downwards, backwards and outwards. The inferior surface of the pterygoid process is divided into two unequal parts by the longitudinal inter-:nal pterygoid process, which projects downwards. This process forms a thin plate prolonged beneath and behind into a hamular process. The hamular processes almost immediately overlie the intersphenoid suture, which marks the anterior end of the avascular area of the sella turcica. Just behind the intersphenoid lies a small emissary vein, which probably marks the obliterated cranio-pharyngeal canal.

(b) OPERATION.

The method of approach, which I employed, was based upon the operation described by McLean (1928). The mouth was held open by means of a gag, and traction was put on the tongue. The soft palate was incised in practically its whole length leaving only about 1 cm of the posterior border intact. The posterior palatine arteries were picked up by forceps. Sutures were passed through the edges of the incision and by this means the edges of the wound were retracted. The mucoperiosteum was divided and stripped from the bone by a periosteal elevator. The posterior edge of the pterygoid lamina was taken as a guide, and by means of a dental drill a hole about 5 mm wide was drilled in the middle line, with the posterior edge of the hole in line with the pterygoid lamina. The bone was drilled through carefully and the dura was ex-:posed. The dura was then incised; a special knife was inserted into the pituitary fossa along its posterior border, and allowed to travel into the brain substance. The special knife which was used was made from a piece of Gillette razor blade 4 mm wide, and with a length of unguarded blade of 1 cm which was fixed firmly into a specially prepared handle.

In all these operations, before drilling the basi-sphenoid, I cut muscle grafts from the temporal muscle, and I found that this was a most effective way of controlling the haemorrhage. Post mortem examination of these cats confirmed that the exposure and division of the hypothalamus were satisfactory. The hypothalamus was divided as far dorsally as the aqueductus cerebri.

10. THE RESULTS AFTER DIVISION OF THE HYPOTHALAMUS.

The operation, which I have described was necessarily from its nature a severe one, and it was rendered more severe because after the hypothalamus had been divided, the skull was then trephined and trauma and local pressure applied to the brain. Fig.23 shows the effect on the blood pressure of a cat during the operation of trephining the basi-sphenoid to expose the hypothalamus; although there has been a drop of the blood pressure, this was not severe. In Fig. 24, A shows where the special knife was introduced through the trephined opening in the basi-sphenoid, and where the hypothalamus was divided. It is seen that the effect of division of the hypothalamus was to cause only a slight drop of blood pressure. B shows the alteration of the posture of the animal. The fall of

blood pressure between B and C was due to the trephining of the skull. At D, pressure was applied to the brain, and this caused a small rise of blood pressure, and at E, the pressure was removed and this was succeeded by a gradual fall of the blood pressure. At F, pressure applied to the brain caused a preliminary rise of the blood pressure, which was followed by a marked fall, and at G, the pressure was removed but the animal died.

Fig. 25 is from another cat and the division of the hypothalamus is shown at A. In this case the animal was getting artificial respiration during the time that the hypothalamus was divided, but the actual division did not cause any fall of the blood pressure. In Fig.26 A shows the division of the hypothalamus, here the blood pressure did not fall, but the respirations became slower.

Fig. 27 shows again the effect of the division of the hypothalamus at A, there being only a very small fall of the blood pressure. Fig. 28 is taken from the same animal after the division of the hypothalamus. At A, pressure was applied to the brain and this caused a marked fall of blood pressure. At B, the pressure was removed and artificial respiration was started. At C, the artificial respiration was stopped and the blood pressure recovered. D shows a repetition of this

procedure. Fig. 29 shows the effect of pressure applied to the brain after the vagi had been divided. At A, artificial respiration was stopped, at B, the vagi were divided, at C, pressure was applied to the brain, at D, the pressure was removed and at E, artificial respiration was started and this was stopped at F, at G, pressure was again applied to the brain. In Fig. 30 artificial respiration was continuous, and pressure was applied to the brain at A and removed at B.

Fig. 31 is a photograph of the brain after removal at post mortem examination. It shows clearly the incision in the hypothalamus and on the surface of the brain the area where trauma was applied to the brain can be seen. This is the brain of the animal from which Fig. 27 was taken.

These experiments show that the actual division of the hypothalamus causes no appreciable fall of blood pressure but may be associated with a slowing of the respiration. When pressure or trauma is applied to the brain after division of the hypothalamus, there is a small preliminary rise of blood pressure, which is not so marked as when the hypothalamus is intact. This rise of blood pressure is followed by a marked fall which is usually

associated with failure of the respiratory centre, and artificial respiration is necessary to prevent the animal dying. After the vagi have been divided in addition to the division of the hypothalamus pressure applied to the brain causes a more marked preliminary rise of blood pressure, which is not followed by a pro-:nounced fall of blood pressure. This result is probably due to the action of the cardio-inhibitory centre being annulled. It would appear from these experiments, that the accessory sympathetic centres which are present in the hypothalamus do not affect the result of trauma or increased intracranial pressure applied to the brain.

11. THE EFFECT OF STIMULATION OF THE HYPOTHALAMUS.

Hasama (1930) has demonstrated by localised fara-:disation the presence of nerve cells in the region of the hypothalamus, which have synaptic connections with the autonomic outflow. Karplus and Kreidl (1927) showed that stimulation of the hypothalamus is followed by a marked increase in the blood pressure. They approached the hypothalamus by removing the cerebral cortex and they stimulated the hypothalamus from above.

When the surrounding brain tissue was stimulated, there was no effect on the blood pressure. Keller (1932) in a study of the autonomic discharges arising on stimula-:tion of mid-brain preparations, exposed the superior colliculi dorsally by retracting one or both occipital lobes lateralad and cephalad. The lesion was made by passing a blunt instrument ventrally into the brain stem at what was judged to be the desired level, care was taken that the instrument passed under the vein of Galen. The tissue cephalad to the section was allowed to remain in place with its blood supply intact.

Van Dijk (1932) attempted to explain the pathways along which impulses set up in the diencephalon of a bird by stimulating that part of the brain with solid sodium chloride or by pressing with the tip of the finger, reach the effector organ i.e. the muscle. The sodium chloride stimulus acts by osmotic forces on the sympathetic centres, analogous to the subthalamic centres which Karplus and Kreidl found in cats, or on some centrally situated part of the sympathetic nervous system. When sodium chloride is applied, the respiratory changes, in contrast with those in the pressure reaction, get faster and the excursions larger. Van Dijk thinks that this is due to stimulation of some centrally situated part of the sympathetic nervous

system. Carbon dioxide poisoning of the respiratory centre, which is regularly found in the pressure reaction, is not a feature of the sodium chloride reaction.

I attempted direct stimulation of the hypothalamus in the cat by removing the skull and drawing forward occipital lobes, but the degree of haemorrhage produced by this procedure was insurmountable, and the blood pressure fell so low that the results obtained were of no value. I also stimulated the hypothalamus by trephining the basi-sphenoid by means of the same technique, which I have described previously for the division of the hypothalamus. The electrodes were then introduced through the trephined opening in the basi-sphenoid and they were passed into the hypothalamus. Fig. 32 is a photograph of the brain of a cat in which this procedure was carried out, and the arrow indicates the position which the electrodes occupied. In the cats in which this was done the stimulation of this area caused very little alteration of the blood pressure but after stimulation had been applied when the distance of the stimulating coil was reduced the cats stopped breathing and died. In Fig. 33 the electrodes were introduced through the opening in the basi-sphenoid into the hypothalamus, and at A this was stimulated with the coil at 20 cm. At

B, the hypothalamus was stimulated with the coil at 10 cm, at C with the coil at 5 cm, and this was repeated at D. At E the vagi were divided and the cat died. In Fig. 34 the hypothalamus was stimulated with the coil at 10 cm, and at B with the coil at 5 cm, at C this was repeated. At D stimulation was again carried out with the coil at 10 cm and this stimulation was maintained for one minute, after an interval the cat stopped breathing and died.

In my experiments I did not get the marked increase in blood pressure on stimulating the hypothalamus, which is described by Karplus and Kreidl. I found that such stimulation, while it might cause a small rise of blood pressure, tended rather to cause a slight fall, and if the stimulus were strong, death of the animal followed.

12. THE EFFECT OF REMOVAL OF THE STELLATE GANGLIA.

Experiments were performed on cats to find out the effect of trauma to the brain and of intracranial pressure applied after both of the stellate ganglia had been removed.

The method of excising the stellate ganglia, which I used, was based on the operation described by Sherrington. The animal was placed on one side, and the fore limb of the uppermost side was drawn forward in the fully extended

condition. A skin incision was made about 7 cm long parallel with and about 2 cm to the right of the mid-:dorsal line. The front end of the incision was on a level with the front of the head of the humerus, the posterior end on a level of the posterior border of the scapula. At each end of this incision a transverse one at right angles to it was made extending from the mid-dorsal line to a point about 7 cm laterally.

The two skin flaps were then reflected and the mus-:cles covering the scapula were exposed. The trapezius was divided near the mid-dorsal line, and the part cover-:ing the suprascapular fossa reflected outwards, and detached from the scapular spine. The rhomboids were then divided and the scapula was displaced laterally. The first rib was located dorsal to the levator anguli scapulae. The origins of the serratus magnus from the posterior border of the first rib, the first intercostal space and from the second rib were reflected laterally. The second rib was then cleared of all attachments as far laterally as possible and its deep surface was gently separated from the underlying pleura, and the portion of rib removed. This was found to be the most difficult part of the operation, as the pleura in the cat is very

thin, and it requires great gentleness and patience to avoid opening the pleura.

The stellate ganglia lies within the first inter-:space covered by fat in tough connective tissue, and a small artery passes obliquely lateral to the ganglion. The ganglion was picked up and in order to excise it the following nerves were divided; (1) the white ramus communicans of the second thoracic nerve, (2) the grey ramus passing towards the first thoracic nerve, (3) from the posterior end the main cord of the sympathetic, (4) a branch from the top of the ganglion, which enters the neck as the cervical sympathetic.

This operation was then repeated on the other side. The double operation was necessarily a severe one, and there was a considerable operative mortality in the cats. After this operation the skull was trephined, and in some cases the brain was traumatised and in others the T shaped brass cannula was screwed into a trephine hole in the skull and the intracranial pressure recorded.

When both stellates had been removed, there was usually a considerable fall of blood pressure due to the operation itself. In the cat from which Fig. 35 was taken, the pleurae were punctured during the operation and this

rendered artificial respiration necessary. It is seen that the effect of local trauma applied to the brain at A., after removal of both stellate ganglia was to cause a small rise of blood pressure, but there was no subsequent fall of the blood pressure owing to the maintenance of the artificial respiration. A later stage of the procedure in the same cat is shown in Fig. 36. At C, both vagi were divided, and following that, severe trauma was used, and this caused a rise of blood pressure followed by a fall which was quickly recovered from owing to the artificial respiration. Fig. 37 was from another cat. Here artificial respiration was continuous, and slight local pressure on the brain did not have any marked effect. The effect of further pressure on the brain in the same cat is seen in Fig. 38.

The effect of trauma to the brain in a cat in which the pleurae were not damaged during the removal of the stellate ganglia is seen in Fig. 39. In this animal the blood pressure was well maintained in spite of the severe operation, at A the skull was trephined and this procedure did not cause a fall of blood pressure, and slight trauma to the brain caused a small rise of blood pressure. Fig. 40 shows the effect of slight trauma to

the brain. In Fig. 41 after division of the vagi, severe trauma was applied and this caused a small rise of blood pressure followed by a marked fall, the respiration ceased and artificial respiration was necessary. Fig. 42 illustrates the same point.

In a number of cats in which both stellate ganglia had been removed, a T shaped brass cannula was screwed into a trephine hole in the skull, and the general intracranial pressure was raised. In Fig. 43 the vagi were intact and the effect of raising the intracranial pressure above the blood pressure was to cause a fall of blood pressure and cessation of respiration necessitating artificial respiration. In Fig. 44 the intracranial pressure was gradually raised, then gradually lowered and the effect was to cause a fall of blood pressure and cessation of respiration. In Fig. 45 the intracranial pressure was gradually raised and maintained for some time, then gradually lowered, there was no marked fall of blood pressure due to the fact that artificial respiration was given as soon as the blood pressure began to fall.

In Fig. 46 the vagi were again intact and the intracranial pressure was gradually raised to 164 mm. Hg, at the commencement the blood pressure was 84 mm. Hg but it gradually rose to 114 mm. Hg. As the intracranial pressure

was raised in this case there was no marked fall of blood pressure, because artificial respiration was continuous. Fig. 47 and 48 show the same effects. In Fig. 49 the vagi were divided, and the results were as before except that in this case the respirations were very slow and spasmodic. As both stellate ganglia were removed and both vagi divided the heart was thus completely denervated.

Fig. 50 is a tracing from a cat in which the stellate ganglia were removed and the vagi were divided, before the intracranial pressure was raised. When the intracranial pressure was raised, there was a preliminary rise of blood pressure followed by a marked fall and cessation of respiration. Fig. 51 was taken from another cat in which the stellate ganglia were removed and the vagi were divided. The intracranial pressure was gradually raised and gradually lowered, the fall of blood pressure was not marked because the intracranial pressure was kept well below the level of the blood pressure. In Fig. 52 the intracranial pressure was gradually raised and then suddenly lowered to zero, and there was a gradual fall of blood pressure, but here again the intracranial pressure never reached the level of the blood pressure. In Fig. 53 the effect is seen of gradually raising and gradually lowering the intracranial pressure,

when artificial respiration is continuous.

These experiments showed that removal of both stellate ganglia has apparently little or no influence on the effect of trauma to the brain. Removal of both stellate ganglia as well as division of both vagi does not materially affect the results. There is still the preliminary rise of blood pressure, followed by a fall and slowing and cessa-:tion of respiration if the trauma has been severe enough, or if the intracranial pressure has been raised sufficiently high. When the influence of the stellate ganglia and vagi nerves has been removed, the heart has had its entire nerve supply cut off, and from this one can conclude that the symptoms which occur during trauma to the brain and increased intracranial pressure are not influenced to any material degree by the heart.

13. THE INFLUENCE OF INTRACRANIAL PRESSURE AND TRAUMA TO THE BRAIN ON THE RESPIRATORY CENTRE.

When the intracranial pressure is increased either as a result of it being artificially raised or as a result of trauma to the brain, the respiratory centre is the first of the vital centres in the medulla to fail. This failure may be associated with a degree of compression, which has no effect on the other vital centres. On prolonged com-

:pression, which causes paralysis of all the centres, the respiratory centre is the last to recover, and, unless artificial respiration is kept up during the compression, the animal will die.

Schmidt (1928) showed that the cerebral blood flow varies with the changes in the systemic blood pressure, and that the cerebral vessels are under intrinsic chemi-:cal control, for they are dilated by carbon dioxide, anoxaemia, acid, heat and cerebral anaemia, and they are constricted by excess of oxygen, alkali, cold, and pro-:bably increased blood flow. On the other hand res-:piration is depressed by an increase in blood flow, even during carbon dioxide inhalation, and stimulated by a decrease no matter how produced, though within certain limits only. Similar results are obtained when the vagi are divided.

The chief function of the entire respiratory mechan-:ism is the maintenance within the centre of a concentra-:tion of stimulant material. Factors which are known to be concerned in this are, changes in the arterial blood through changes in pulmonary ventilation, acid excretion by the kidneys, changes in the metabolic activity of the centre and changes in the blood supply of the centre.

Respiratory activity at any instant depends upon a delicate equilibrium between these factors.

There are at least five theories of the mode of action of lack of oxygen on the respiratory centre, (1) direct ac-:tion on the respiratory centre, (2) regulation of the excitability of the centre to normal respiratory stimuli, (3) indirect stimulation of the respiratory centre through the formation of lactic acid which, reaching the blood, lowers the alkali reserve and raises its H ion concentra-:tion, (4) indirect stimulation of the respiratory centre through the formation of lactic acid within the centre itself, (5) indirect stimulation of the respiratory centre by the formation of easily oxidisable substances, other than acids, which during lack of oxygen reach the blood and pass through the lungs in excessive amounts and excite the centre.

The theories of the mode of action of carbon dioxide are, (1) stimulation by virtue of its effects on H ion concentration of the blood, (2) stimulation by virtue of its effects on H ion concentration of the cells after having entered the cells, (3) stimulation by virtue of a specific effect other than changes in the H ion concentra-:tion.

Gesell (1923) thinks that the activity of the respira-:tory centre is fundamentally a function of its own acidity, as opposed to the acidity of the arterial blood and direct stimulant effect of lack of oxygen. By virtue of its sensitivity to the H ion concentration, the respiratory centre responds to the changes in its own acidity as in-:fluenced by its own acid metabolism. The changes in acidity of the respiratory centre constitute the primary control of respiration.

When increased intracranial pressure reaches the subtentorial space it causes venous stasis of the capillaries of the medulla together with stimulation of the respiratory centre. When the intracranial pressure is further increased the medullary capillaries are emptied and anaemia results with the consequent failure of the respiratory centre.

PART II.

1. INTRODUCTION.

The second part of the investigation deals with the possibility of a chemical substance or substances which may be present in the brain, possibly exercising a de-:pressor action on the blood pressure, if they are liberated into the blood stream, when the brain is in-:jured, and thereby causing shock-like symptoms. Among the solid constituents of nervous tissue are proteins cholesterol, cerebrosides, lecithin, kephalin, nuclein, collagen and inorganic salts. The proteins are present in the greatest amount and comprise of about 50% of the total solids.

As long ago as 1896 Schäfer and Moore, while working on the contractility of the spleen, gave intravenous in-:jections of various animal extracts, and they found that an extract of dried brain made with boiling water or saline solution when injected was followed by a fall of blood pressure. Mott and Halliburton (1899) suggested that this material was choline.

In 1900 Osborne and Swale Vincent found that the fall of blood pressure, which was caused by the brain extract, was affected neither by the division of both

vagi nor by the administration of atropine, and that the lowering of the blood pressure was due to dilatation of the arterioles, those of the splanchnic area being af-:fected first. They expressed the opinion that the depressor substance acted directly upon the blood pres-:sure and not through the agency of the vaso-motor nerves. They also formed the opinion that this depressor action was not due to choline. Best, Dale, Dudley and Thorpe (1927) showed that tissue extracts, which exerted a de-:pressor influence, owed their physiological activity largely to histamine and choline.

Recently two papers have been published which deal with the presence of depressor substances in the brain. Firstly "A Comparison of the Properties of Certain Tissue Extracts having Depressor Effects" by Major, Nanninga and Weber (1932), and secondly "The Presence in the Brain of a Substance resembling Acetyl Choline" by Dikshit (1933); but I had started my investigation along these lines before either of these papers had been published.

It is at present generally believed that secondary shock is due to histamine, which is liberated in the body, and it was to this substance that I first of all directed my attention. The other possibility that suggested itself was the substance known as acetyl choline.

2. HISTAMINE.

Histamine or β-iminazole-ethylamine is a product of the putrefaction of histidine, which is β-iminazole-α-amino-propionic acid, and which is one of the amino acids present in proteins. Histamine is a constituent of ergot, and is present in putrefied meat. It is formed by the decarboxylation of histidine.

It has been suggested that histamine exists either in loose combination with another substance or that it exists in the cells from which it is liberated by physi-:cal or chemical means. The simplest extract of fresh tissue yields histamine and there is thus reason for re-:garding it as a constituent of normal tissue. It has been definitely isolated from normal animal tissues. It is interesting to note that Dragstedt (1928) in a study of the blood chemistry in intestinal obstruction emphasizes the similarity between the effects of injec-:tion of the obstruction fluids and of histamine. But Mellanby (1915) found that histamine may be present in the mucosa and in the contents of unobstructed bowel. In a closed loop of intestine in animals, he found sub-:stances accumulated which had many physiological and chemical properties similar to histamine. He also

found that histamine could be absorbed from the small or large intestine of animals or when administered orally to human beings, but he was of the opinion that there was no ground for believing that it played an important role in the pro-:duction of the signs and symptoms of simple intestinal obstruction.

Histamine was first isolated from animal tissues (the intestinal mucosa) by Barger and Dale (1911). It is liberated in the body even by minor injuries to the tissues and this was demonstrated by Lewis (1927) who has brought forward evidence to show that heavy stroking of the skin causes the liberation locally of substances with a histamine-like action, this he calls the "H" substance. Any injury of the skin in fact, such as scratching, freezing, burning or the application of a substance like cantharides liberates histamine. It is doubtful if histamine is present in the blood. Koessler and Hawke (1924) were unable to find any in the human blood. On the other hand, Harris (1927) on physiologi-:cal assay said that the blood contained 0.5 mg histamine per kilogramme. Although histamine is said to be a constituent of animal tissue I have not been able to find any reference in the literature to its presence in the

brain except that Dale and Dudley (1921) state that it is present in small amounts in pituitary extracts, but was present in such small amount that it could not be detected chemically.

The main action of histamine is on the circulatory system. Dale and Laidlaw (1910) found that small doses of histamine increased the force and frequency of the heart beat of rabbits and cats, and that larger doses caused a weakening of the heart. Fuhner and Starling (1913) reported a rise in the pulmonary arterial pressure when large doses of histamine were added to the blood in the heart lung preparation of a dog. Oppenheimer (1929) compared the effect of certain heart extracts and of histamine on the isolated perfused heart of the rabbit, and the results were very similar, namely an increased amplitude and in many cases an acceleration of the rate of the heart beat, followed subsequently by a diminution of the rate and failure of the heart. Hashimoto (1925) showed that intravenous administration of large doses of histamine to dogs caused a delay in the auriculo-ventricular conduction, and a temporary partial or complete heart block. Dixon and Hoyle (1930) observed an increased cardiac output in the cat with small doses of histamine, while large doses

produced diminution and when the blood pressure had fallen considerably the heart dilated. Gunn (1926) found that histamine produced a dilatation of the coronary vessels in the cat's heart. The evidence suggests that small doses of histamine have little if any effect on the heart, while larger doses increase the force and rate of the heart in most species.

Dale and Laidlaw (1910) showed that intravenous injection of histamine produced profound lowering of the blood pressure in the anaesthetised cat. Dale (1919) showed that this effect is not produced even when relatively large doses are slowly run into a vein of an unanaesthetised cat, and he has given as much as 10 mg per kilogramme weight with only temporary and mild symptoms. Presumably the anaesthetic in some way sensitizes the capillaries to histamine. McDowall (1923) showed that small doses of histamine produced a rise of venous pressure in cats under light anaesthesia and when the anaesthesia was deepened this effect of histamine was not observed.

Dale and Richards (1918) found that preparations made from the cat's mesentery, the vessels of which are arterial, showed constriction after histamine had been added to the perfused fluid. Burn and Dale (1926) observed that in a

similar preparation from the dog, histamine produced some dilatation. In man and monkey it produces dilatation of the arterioles.

Hooker (1921) made direct observations on the effect of histamine on the capillaries and venules of anaesthetised cats. He found that within a few minutes of the injection of large doses both types of vessels were dilated and filled with stagnant blood. Rich (1921) using the omentum of etherised cats found that the injection of histamine excited a local vaso-dilator effect upon the capillaries, the small arterioles and the venules, and new capillaries were observed to open up under the influence of histamine.

Florey and Carlton (1926) observed the mesentery capillaries under saline in anaesthetised cats, and found that the injection of histamine into the saphenous vein produced a dilatation of the capillaries and an opening up of many which have not been previously apparent. In addition to these actions, histamine has a powerful secretagogue action, but in man this action is limited mainly to the gastric glands. It is also a stimulant of the smooth muscle, e.g. intestinal wall, uterus and bronchioles.

3. ACETYL CHOLINE.

Choline or hydroxy-ethyl-trimethyl-ammonium hydroxide is a trimethylamine derivative of ethyl alchohol, and occurs in the free state in most animal tissues and is also widely distributed in plants.

It is closely related chemically to muscarine, which is a very poisonous base obtained from certain fungi. Lecithin, when hydroylised, yields oleic acid, which is an unsaturated fatty acid, stearic acid, which is a saturated fatty acid, glycerol, which is a triatomic alchohol, phos-:phoric acid and choline.

Le Heux (1919) and Magnus (1930) have shown that there is evidence that the intestine is capable of esterifying choline in the presence of appropriate anions to form highly active choline esters.

Recently the "humoral theory" of nerve action has been proposed. By this is meant that if one nerve influences either a viscus or another nerve it does so by the libera-:tion of a particular chemical substance. According to Loewi (1921) the vagus acts by producing some chemical substance, which is not potassium but which has the power of depressing the activity of different parts of the heart. It is thought that this so called "vagus substance" is

acetyl choline, and that the effect of vagus excitation is to produce or liberate this substance in the immediate vicinity of the vagus endings.

Acetyl choline imitates the action of the parasympa-:thetic, as it slows the heart and stimulates intestinal movements. If the motor nerve supply of the hind limbs of a cat be severed and allowed to degenerate, the injec-:tion of acetyl choline produces a slow contraction of the voluntary muscle. Stimulation of the peripheral end of the posterior nerve roots produces a similar action in the denervated muscles of the hind limb of the cat. The fact that both acetyl choline and posterior roots stimu-:lation produce the same two effects in the hind limb, i.e. vaso-dilatation, and this slow contraction of the denervated muscle has led to the suggestion that the posterior nerve roots may also liberate acetyl choline peripherally. It is of interest to note that after atropine the vagus can still stimulate the movements of the intestine, and the chorda tympani still produces vaso-dilatation, but the similar actions of acetyl choline are abolished.

Dikshit (1933) used extracts of the brain of cats and rabbits. The brains were macerated with acid-water-acetone mixture, filtered, the filtrate evaporated

to dryness and the residue dissolved in water. These extracts produced actions similar to those of acetyl choline, when tested on the blood pressure of cats and on isolated rabbit's gut. These actions were com-:pletely abolished by atropine and were also rendered inactive by an esterase isolated from horse serum,which had been shown by Stedman, Stedman and Easson (1932) to have a specific action of destroying acetyl choline. Dikshit pointed out that the concentration of acetyl choline was greatest in the basal ganglia and least in the cerebellum, and that the cortical portion of the brain had a concentration slightly lower than that pre-:sent in the basal ganglia.

Major, Nanninga and Weber (1932) extracted a depressor substance from the brain. They also pointed out that extracts from the basal ganglia were more active than extracts from other parts of the brain, but they are of the opinion that this substance is neither histamine nor choline, because atropine abolishes the action of choline but had no effect upon the brain extract. They used a method of making the brain extract something similar to that employed by Dikshit, although their conclusions are dissimilar. This discrepancy in the

results may possibly be due to the technique. In some of my experiments with intravenous injection of brain ex-:tract, it was noted that the results were not consistent with those of previous experiments, and it was found that even Burn and Dale's solution caused a fall of blood pressure and this was proved to be due to an error in the technique. In these particular experiments, hista-:mine, brain extract and other substances had been injected in rotation into the jugular vein through a cannula, and a fall of blood pressure was obtained with substances which should not have caused a fall. That this was due to minute traces of histamine or of the depressor substances in the brain extract remaining in the cannula, was proved by the subsequent thorough sterilisation of the apparatus and by injection directly into the saphenous vein of the hind limb. This goes to show that if the results of animal experiments are to be considered reliable a very careful technique involving surgical cleanliness is necessary.

In addition to the acetone method, Major, Nanninga and Weber used some elaborate chemical procedures for purifying the brain extract, such as the method of Felix and Putzer-Reyberg (1932) for the fractional

precipitation with silver: saturated alchoholic solution of mercuric chloride, made alkaline and the precipitate removed; they also purified the extract with Lloyds reagent and alchohol. There is a possibility that these complicated methods may alter the constitution of the substances in the brain extract.

The use of the frog's rectus abdominis muscle as a test for the presence of acetyl choline was first described by Reisser (1921). The muscle from Rana Escalenta is rather more sensitive than that obtained from Rana Temporaria, but either species can be used. Chang and Gaddum (1933) also recommend the use of the rectus abdominis muscle of the frog or the longitudinal muscle of the leech as suitable objects for testing for acetyl choline in tissue extracts. The frog's heart may also be used. The extracts must be neutralised, as small quantities of acid produce effects similar to that of acetyl choline. It is not yet definitely known if normal blood contains acetyl choline. Kapfhammer and Bischoff (1930) claim that the blood does contain large quantities of acetyl choline, but on the other hand, Dudley (1933) has consistently failed to detect physiologically more than the merest traces of

substances resembling acetyl choline in blood extracts at any stage of the process of purification.

Taveau and Reid Hunt (1906) state that acetyl choline as regards its effect on the circulation is the most powerful substance known. It is 100,000 times more active than choline, and hundreds of times more than active in causing a fall of blood pressure than nitro glycerine. It is one hundred times more active in causing a fall of blood pressure, than adrenalin is in causing a rise. Reid Hunt (1918) has shown that as little acetyl choline as 0.000,000,0024 mg per kilogramme caused a pronounced fall of blood pressure.

Carmichael and Fraser (1933) point out that the action of acetyl choline in animals suggests that its effects are closely similar to those of stimulation of the parasympathetic system, and when the parasympathetic system is stimulated, a substance closely related to acetyl choline is concerned in the effects produced by this stimulation. Dale (1914) has shown that its action in cats is closely parallel to those produced by stimulation of the parasympathetic nerves.

4. EXPERIMENTAL WORK.

Three methods were used in the experimental work designed to detect the presence of chemical substances in the brain. The first method employed was to inject extracts of brain intravenously in cats in which the blood pressure was recorded on the moving drum from the carotid artery, and also to record the respiratory move-:ments by means of the specially designed stethograph, which I have already described. In some of the experi-:ments a glass cannula was introduced into the jugular vein, and at the end of the cannula a piece of rubber tubing was attached and this was clamped at its free end by means of a clip. The needle of the syringe was passed into the rubber tube and the soluction in-:jected, and immediately afterwards saline solution was injected in a similar manner in order to wash in any of the solution which might have remained in the cannula. In other animals the solutions were injected directly into a vein, usually the saphenous vein. In all these experiments the greatest care was taken to have the needles and syringes sterile and the procedures were as far as possible carried out under aseptic con-:ditions. In the second method the brain extracts were tested in the bath against the virgin uterus of

the guinea pig and the small intestine of the cat. In the third method various physiological tests for acetyl choline were applied to the cat.

The method of preparing the extract from the brain was as follows: the brain tissue was pounded up with acetone, and for each gramme of brain 1 cc of acetone was used. After the brain extract had been thoroughly pounded, the mixture was evaporated in a water bath, and the residue was extracted with distilled water. This I have called No. 1 Brain Extract. In an attempt to produce further purification of the brain extract another method was used. The aqueous extract (No. 1) was acidi-:fied with 5% acetic acid, and then saturated with picric acid and after half an hour was filtered. The filtrate was extracted with ether until no yellow colour of picric acid was left. The ether was then boiled off and the solution was neutralised with NaOH. This was called No. 2 Brain Extract, but no difference was detected in the results of these extracts.

In some of the earlier experiments a portion of the cat's own brain was removed and ground up with sand stirred up in Tyrode solution and filtered, and this was used for intravenous injection, but the results from this method were not satisfactory, partly owing to the

method of preparation and partly to the haemorrhage, which was associated with the partial removal of the brain. In other experiments the animals were decerebrated, and ex-: tracts from the animal's own brains were made with the acetone and picric acid methods as described above. In most of the experiments fresh ox brain was used. It was thought that by using the animal's own brain there would be no risk, in event of any proteins remaining in the ex-: tract, of a fall of blood pressure from that cause, since the animals own proteins would not cause a fall of blood pressure. The tracings in Fig. 54 show the effect of the injection of such an extract. This cat was a male weighing 4.4 K, a record of the blood pressure was taken from the carotid artery and the animal was decerebrated. After decerebration the animal was left for some time in order to allow the ether to blow off. In this animal the blood pressure after decerebration was 180 mm. Hg. In tracing A at the first arrow 0.5 cc. of the extract of the cat's own brain was injected into the left jugular vein, and the immediate result was a sharp drop of blood pressure from 180 mm. Hg. to 80 mm. Hg., as the blood pressure reached 80 mm. Hg. the respirations became in-: creased in amplitude and rate, The blood pressure then gradually recovered to its original level and when

this point was reached the respiration settled down normally. Tracing B shows the effect of repeating the same dose as in A. Tracing C shows the effect of injecting 0.5 cc. of the No. 2 extract of the brains of other two cats. In this case the brain of the two cats weighing 50 grammes were extracted, the quicker recovery in this case may have been due to the fact that the dry extract had been prepared five days previously. Fig. 25 was a male cat weighing 3.6 K, it was decerebrated at 8.55 a.m.and left until 2.30 p.m. before the rest of the experiment was carried out. At A, 0.5 cc. of No. 1 brain extract was injected. It will be noticed that there was a considerable delay before the blood pressure fell, but this was due to the fact that the vein became twisted during the injection. At B, 1 cc. of saline solution was injected to wash in any of the extract remaining in the cannula. The effect on the respiration was the same as before, except that the respirations in this cat were slower. This animal developed Traube Hering Waves as shown in the tracing. In Fig. 56, A shows the effect of the injection of 1 cc. of No. 1 brain extract, B the effect of 1 cc. of saline, and this gave the same

results as before. Traube Hering Waves are still pre-:sent. Up to this stage the animal being decerebrated was not getting any anaesthetic, but before the next tracing Fig. 57 the animal was given intracheal ether for some time and then the ether was blown off and at A, 0.5 cc. of No. 1 brain extract was injected and at B, 1 cc. of saline. It is to be noted that the ef-:fects are the same as before but that the respirations are more rapid.

Fig. 58 was a tracing from a female cat weighing 3.4 K, the blood pressure was taken from the left carotid artery; in this case the brain was not touched but a fresh ox brain weighing 300 grammes was used. At A, 0.25 cc. of No. 1 brain extract was injected and this caused a fall of blood pressure, which recovered gradually. Before the injection the animal was breath-:ing rapidly, and the injection had no appreciable effect on the respiration, but in this case the dose was only half of that given in the previous experiment. In Fig. 59 A indicates the injection of 0.5 cc. of No. 1 brain extract, B, the injection of 0.5 cc. of saline, C, the injection of 1 cc. of No. 1 brain extract and D, the injection of 0.5 cc. of saline. The larger dose

caused a marked alteration of respiration. In Fig.60 both vagi were divided some time before the injection of 1 cc. of No. 1 brain extract at A, B shows the injec-:tion of 0.5 cc. of saline. This shows that division of the vagi, apart from altering the respirations, does not materially affect the results. Fig. 59 which was taken from the same animal as Figs. 58 and 60 shows the injection of the same dose before the vagi had been divided.

These tracings showed that in decerebrate animals the blood pressure falls immediately the injection is given, but in animals in which the brain is intact there is a latent period between the intravenous injection and the fall of blood pressure. These tracings which are representative of many other experiments show that there is some depressor substance or substances present in the brain. That this substance is not protein is shown by the fact that when the animal's own brains were used, a fall of blood pressure still occured and autogenous pro-:teins would not cause this result, and also that the method used in the preparation of the extract removes the proteins.

The next step in the investigation was to attempt to determine the nature of this substance. As the pre-

:sence of histamine in the body is almost universal, although as I have previously mentioned I have not been able to find any reference to the presence of histamine in the brain, apart from small quantities in the pituitary body, the procedure adopted was to make an attempt to see if this fall of blood pres-:sure were caused by histamine. In all the experiments in which brain extracts were employed, great care was taken in the preparation of the ex-:tracts to exclude the pituitary body, so that the results would not be due to histamine from the pit-:uitary body or to other pituitary extracts. The results of the injection of a small dose of histamine is seen in Fig. 61. This tracing was taken from a male cat weighing 2.4 K., the blood pressure was taken from the femoral artery. An extract was prepared from the damaged muscles of a crushed limb which had been amputated in hospital. At A, a very minute dose of this extract was injected intravenously and this caused a fall of blood pressure, and at B, a larger dose of the same extract was injected and this gave a more marked fall of blood pressure. This ex-:tract most probably contained histamine. At C, 0.00002 mg. histamine was injected and at D, the same

dose of histamine was repeated, in both cases this caused a marked fall of blood pressure.

One of the difficulties of recognising histamine is that there is no satisfactory test for identifying it, except the physiological test. There is, however, a substance called "Norit", which is very useful in this connection. This substance, Norit, is a vegetable charcoal which is used commercially for decolourizing sugar, but in addition it possesses the power of adsorbing histamine, and it acts by surface action.

Fig. 62 shows the effect of an injection of very small doses of histamine in a male cat weighing 3.6 K. At A, 0.3 cc. of 1 in 100,000 solution of histamine was injected, and it caused a definite fall of blood pressure. B shows where the drum was stopped, and at B, 0.3 cc. of 1 in 100,000 solution of histamine, after it had been treated with Norit, was injected,and it shows that there is now no fall of blood pressure proving that the histamine has been entirely adsorbed by the Norit. I also tested the effect of Kaolin on histamine but it was found to have no powers of adsorption.

After demonstrating that Norit does adsorb histamine, it was next tested against the brain extract. Norit was

added to the brain extract and the mixture was shaken and allowed to stand for some time and then filtered, and the filtrate was used for the injection. In Fig. 63, A indicates the injection of 0.25 cc. of brain extract and B, the injection of brain extract after it had been treated with Norit. It will be seen that after treatment with Norit the brain extract caused only a very slight fall of blood pressure. Fig. 64 was taken from another cat, A indicates the injection of 0.5 cc. of No. 1 brain extract, and B the injection of 1 cc. of saline. C shows the injection of 0.5 cc. of No. 1 brain extract after it had been treated with Norit, here again there was a slight fall of blood pressure, but this was only trivial as com-:pared with the same amount of the brain extract when it had not been treated with Norit. In still another cat Fig. 65, A indicates the intravenous in-:jection of 0.5 cc. of brain extract and this shows clearly the quickening of the respirations. B shows the injection of a similar amount after treatment with Norit, here again there is only a very slight fall of blood pressure. In Fig. 66, A shows the effect of the intravenous injection of 1 cc. of brain extract

and B shows the injection of a similar amount after treat-:ment with Norit, and Fig. 67 shows at A the result of the injection of 0.5 cc. of brain extract after treatment with Norit. Fig. 68 was taken from a female cat weighing 2.3 K., the injections were made directly into the saphen-:ous vein. A shows the effect of the injection of 0.3 cc. of brain extract and B, the injection of the same quantity after treatment with Norit. In this case on the first injection there was a marked fall of blood pressure with very considerable upset to the respirations, the fall after treatment with Norit was also apparent but not marked when compared with the first injection. In the tracings the degree of the fall of blood pressure varied in different cases, this being probably due to the individual idiosyn-:crasies of the different cats.

The tracings described were selected from those of a series of experiments in which brain extracts were used in 22 cats, and they show clearly that the intravenous injection of brain extract causes a marked fall of blood pressure, and that this fall of blood pressure resembles that produced by the injection of histamine, but that after the brain extract has been treated with Norit, the fall of blood pressure which is produced is only trivial.

This means that the Norit has adsorbed some substance present in the brain extract which resembles histamine. At a later stage in this thesis, I have attempted to show by further physiological tests that this substance is histamine or at least a histamine-like substance, resembling that which Lewis designated the "H" substance.

While Norit, when added to histamine, adsorbs all the histamine present, when it is added to the brain extract, there still results a very slight fall of blood pressure on intravenous injection. Assuming that the substance in the brain extract is histamine, then it should be entirely adsorbed by the Norit, and this would mean that the slight fall of blood pressure still present is due to some other substance. An attempt has been made later to show that this substance is probably acetyl choline.

The second method used in this part of the investigation was to make attempts to prove further that histamine and acetyl choline were present in the brain extracts and for this purpose the uterus of the virgin guinea pig and the small intestine of the cat were used. The apparatus used for this purpose was that of Trendelenburg and it is shown in Fig. 69. The only difference in the apparatus

that I used was that a specially designed lever was employed. The apparatus consisted of an inner vessel (1) which con-:tained the nutrient fluid; an outer reservoir (2) with hot water, which contained a thermometer (13). Below the reservoir was a lamp house, (8) which contained a carbon filiment lamp (9) to keep the temperature constant. Con-:nected with the inner vessels was an outlet (3) by means of which the bath was washed out into the receiver (10). The apparatus was connected with a pressure bottle (7), which contained a mixture of carbon dioxide and oxygen, by means of a T shaped tube this was connected with the aerater (4) and this had a curved end which was fastened to the tissue under examination. The other end of the piece of tissue was attached by a thread to the writing lever (11), at the free end of which there was attached a hedgehog quill point. The nutrient fluid which was used for the uterus was that recommended by Burn and Dale, except, that glucose was not added. It consisted of

NaCl	.....	0.9%
Kcl	.....	0.042%
$NaHCO_3$	.....	0.05%
$NgCl_2$	.....	0.0005%
$CaCl_2$	.....	0.024%

the fluid used for the small intestine of the cat was Tyrode-Bayliss solution

NaCl	..... 0.8%
KCl	..... 0.02%
$CaCl_2$	..... 0.02%
$NaHCO_3$	..... 0.1%
$MgCl_2$	..... 0.01%
NaH_2PO_4	..... 0.005%

The guinea pigs used in these experiments were bred specially for the purpose. A strip of tissue from the cornu of the virgin uterus was suspended in the bath. The brain extract was prepared in the same way as for the previous experiments. In Fig. 70, A indicates the addition to the water in the bath of a 1 in 1,800,000 solution of histamine and shows the extent of the contraction of the uterus which this dose of histamine caused. B shows the effect of the addition to the bath of 0.5 cc. of No. 1 brain extract, and as the uterine muscle did not relax the bath was washed out. It will be noticed that the contraction caused by the histamine is similar to that caused by the brain extract. Fig. 71 shows the contraction caused by the addition to the bath of a 1 in 10,000,000 solution of histamine and by 1 cc. of No. 1 brain extract

and 1 cc. of No. 2 brain extract. Fig. 72 shows the contraction caused by a 1 in 10,000,000 solution of histamine and by 1 cc. of No. 1 brain extract and 1 cc. of No. 2 brain extract, and also by 1 cc. of No. 1 brain extract after treatment with Norit. It will be noticed that after the histamine had been removed by the Norit the extract still caused a contraction, this was probably due to the acetyl choline which is probably present in the brain extract.

Fig. 73 was taken from another virgin guinea pig of which the uterus was used; (1) shows the contraction caused by the addition to the bath of 0.5 cc. of a 1 in 10,000,000 solution of histamine, and (2) shows where the bath was washed out. (3) indicates where 0.25 cc. of No. 1 brain extract was added and (4) where the bath was washed out. (5) indicates the addition of 0.25 cc. of No. 1 brain extract after treatment with Norit and this caused a contraction which was sustained. At (6), the uterus was still contracted and at this point 1 cc. of 1 in 100,000 solution of atropine was added to the bath and very shortly afterwards the uterus relaxed. It is known that atropine abolishes the action of acetyl choline, and atropine was added because, if the contraction

were due to acetyl choline, the atropine should antagonize the acetyl choline and therefore cause relaxation of the uterine muscle, and this is what actually did happen. At (7) the bath was washed out. Then the action of pure acetyl choline was tested. At (8), 0.008 gramme of acetyl choline was added to the bath and this caused a contraction of the muscle, and the muscle continued in the contracted state. At (9), when the muscle was still contracted, atropine was added to the bath, and after a short interval the muscle relaxed. The contraction and relaxation closely resembled the previous one where brain extract was used.

These experiments indicate that probably not only histamine but also acetyl choline is present. Fig. 74 illustrates a further stage in the investigation. Again the virgin uterus was used, (1) shows the contraction of the uterus by a very small dose of histamine (0.25 cc. of a 1 in 1,000,000 solution of histamine). At (2) the bath was washed out and at (3) 0.25 cc. of brain extract was added. At (4) the bath was washed out and at (5) 0.25 cc. of brain extract, after treatment with Norit, was added, and the result was a contraction resembling (3), but not so marked, because in this case the histamine had

been removed by the Norit. At (6) the bath was washed out, and at (7) 0.25 cc. of a 1 in 1,000 solution of atropine sulphate was added, this was not washed out, and at (8), 0.25 cc. of brain extract after treatment with Norit was added. In this case it has to be noticed that there was no contraction of the uterine muscle, this was presumably because the brain extract had been previous-:ly treated with Norit, and thus the histamine was removed, leaving behind what was presumed to be acetyl choline in view of the previous experiments. Owing to the presence in the bath of the atropine which had already acted on the uterine muscle, and which, as has been previously pointed out, antagonizes the action of acetyl choline, the acetyl choline was rendered functionless and consequently both the histamine and the acetyl choline having been removed, there was no contraction of the muscle. At (9) the bath was washed out, at (10) 0.00156 gramme of acetyl choline was added to the bath and this caused a contrac-:tion, there being now no atropine present. At (11) the bath was washed out and at (12) 0.00156 gramme of acetyl choline, after treatment with Norit, was added and this resulted in a contraction. This was done in order to see if the Norit had any effect on acetyl choline, but

the result shows that the action of acetyl choline is not affected by Norit. At (13) the bath was washed out, and at (14) (12) was repeated, this time the contraction was even more marked. At (15) the bath was washed out and at (16) 0.00156 gramme of acetyl choline was added and a contraction resulted. At (17) the bath was washed out and at (18) 0.25 cc. of a 1 in 1,000 solution of atropine sulphate was added, at (19) 0.00156 gramme of acetyl choline was added, but owing to the presence of the atropine, no contraction resulted. The upstroke at (19^a) is due to the bath being washed out. At (20), (12) was repeated and at (21) the bath was washed out.

These experiments indicate that atropine inhibits the action of acetyl choline, and that in the brain extracts after the histamine has been removed by the Norit, atropine inhibits the action of the substance remaining, which closely resembles and most probably is acetyl choline.

In another series of experiments the small intestine of cats was used and this reacts differently both to histamine and acetyl choline from the virgin uterus. Neither of these substances causes a marked contraction in the small intestine of the cat, but the action of

histamine on it is so powerful that it practically paralyses the bowel. In these experiments the cats were killed by chloroform and the intestine was removed immediately and a portion of it was suspended in the bath as before. Fig. 75 illustrates an experiment in which the small intestine of the cat was used. At (1), 1 cc. of brain extract was added to the bath and it gave a very feeble contraction and at (2) the bath was washed out. At (3) 1 cc. of brain extract after treatment with Norit was added, and this gave practically no contraction. At (4) the bath was washed out and at (5) acetyl choline was added and this gave a distinct contraction until the bath was washed out at (6). At (7) acetyl choline, after treatment with Norit, was added, and this shows that acetyl choline is not affected by the Norit. At (8) the bath was washed out, at (9) 2 cc. of brain extract was added and at (10) the bath was washed out. At (11) 2 cc. of brain extract, after treatment with Norit, was added and this caused a contraction which was sustained until (12) when the bath was washed out. This contraction resembles (5) and (7), where acetyl choline was added, and is probably due to the fact that the Norit has removed the histamine and thereby its toxic effects and the resulting contraction is caused

by the acetyl choline present. At (13) 0.5 mg. atropine sulphate was added and at (14) without washing out the bath 1 cc. of brain extract, after treatment with Norit, was added and there was no result, this being due to the atropine having inhibited the acetyl choline.

In the experiment illustrated by Fig. 76 the small intestine of a kitten was used. At (1) 1 cc. of a 1 in 100,000 solution of histamine was added and at (2) the bath was washed out. At (3) 0.25 cc. of acetyl choline (1 cc. = 0.006 gramme) was added and this caused a contraction, and the intestine did not relax until the bath was washed out at (4). At (5) 1 cc. of brain extract was added and the bath was washed out at (6), at (7) 1 cc. of brain extract, after treatment with Norit, was added, and the bath was washed out at (8). At (9) 0.25 cc. of acetyl choline, after treatment with Norit, was added, and the bowel remained contracted until the bath was washed out at (10). At (11) 0.3 cc. of 1 in 1,000 solution of atropine sulphate was added, and at (12) 1 cc. of brain extract, after treatment with Norit, was added but this gave no result because the atropine had inhibited the action of the acetyl choline.

At (13) the bath was washed out.

In Fig. 77 the small intestine of a cat was again used. (1) shows the effect of 1 cc. of 1 in 1,000 solution of histamine, and at (2) the bath was washed out. At (3) 0.008 gramme of acetyl choline was added and it caused a marked contraction of the intestine, which did not relax until the bath was washed out at (4). At (5) 2 cc. of brain extract were added to the bath and this caused a contraction, at (6) the bath was washed out. At (7) 1 cc. of 1 in 1,000 solution of histamine together with 0.0004 gramme of acetyl choline were added, and the result here closely resembled (3), where acetyl choline alone was added. At (8) the bath was washed out, and at (9), 2 cc. of brain extract, after treatment with Norit, were added and the bath was washed out at (10). At (11), 1 cc. of 1 in 1,000 solution of atropine sulphate was added, and at (12) 1 cc. of brain extract, after treatment with Norit, was added and this gave no contraction.

Fig. 78 illustrates another experiment in which the small intestine of the cat was used. (1) shows the effect of the addition to the bath of 0.5 cc. of a 1 in 100,000 solution of histamine, and at (2) the

bath was washed out. At (3) 0.004 gramme of acetyl choline was added to the bath with the same result as before. At (4) the bath was washed out, at (5) 2 cc. of brain extract were added and at (6) the bath was washed out. At (7) 0.5 cc. of 1 in 100,000 solution of histamine together with 0.0004 gramme of acetyl choline were added, and the bath was washed out at (8). At (9) 2 cc. of brain extract, after treatment with Norit, were added, and this was the same amount of brain extract as in (5), there is, however, a marked difference; in (5) the "H" substance is still present and has presumably more or less paralysed the intestine, in (9) the "H" substance has been removed by the Norit and the resulting contraction is presumably due to the acetyl choline substance. At (10) the bath was washed out and at (11) 0.1 cc. of 1 in 1,000 solution of atro-:pine sulphate was added, and at (12) 2 cc. of brain extract, after treatment with Norit, was added, and no contraction resulted owing to the action of the atropine on the acetyl choline, here of course the histamine had been removed by the Norit. At (13) the bath was washed out and at (14) 0.3 cc. of atropine sulphate was added and at (15) 0.0004 gramme of acetyl choline was added,

and here again the atropine prevented a contraction of the intestine. At (16) the bath was washed out and at (17) 1/100,000 gramme of eserine salicylate was added to the bath, at (18) 2 cc. of brain extract, after treatment with Norit, were added, and the figure shows the resultant rhythmical contraction; eserine is supposed to prolong the action of acetyl choline.

These experiments with the small intestine of the cat show:-

(1) That histamine does not cause a contraction of the small intestine.

(2) That acetyl choline causes a marked contraction of the intestine and that the intestine remains contract-:ed until the bath is washed out.

(3) That when the brain extract is added a contraction results, but that when the brain has been treated with Norit, a contraction still results showing that it is due to the acetyl choline present, and not to the histamine as it has been removed by the Norit.

(4) That the contraction caused by the brain extract is a small contraction, which relaxes of its own accord, but that after the brain extract has been treated with Norit the resulting contraction is maintained until the bath is washed out. This is probably because when the brain extract alone is used the "H" substance which is present more or less paralyses the intestine, but that after it has been treated with Norit, this "H" substance is removed and the resulting contraction is due to the acetyl choline substance.

(5) That after atropine has been added to the bath neither the brain extract nor pure acetyl choline cause a contraction.

These experiments in which the small intestine of the cat was used confirm those in which the uterus of the virgin guinea pig was used. It seems justifiable

to conclude that there are at least two depressor substances present in the brain extract namely histamine and acetyl choline or substances closely resembling them.

In the third group of experiments, the various physiological tests for acetyl choline were applied. Intravenous injections were made in cats in which a record of the blood pressure was taken. Chang and Gaddam (1933) point out that there are several special tests which may be used to differentiate between the effects due to acetyl choline and those due to other substances. Eserine should increase the action of acetyl choline, but not the action of choline. The activity of acetyl choline should disappear rapidly, when the extract is mixed with blood. This is due to the presence in the blood of an esterase which is supposed to destroy acetyl choline. Acetyl choline should be unstable in alkaline solution; and atropine antagonizes acetyl choline.

Some of these tests have already been applied in the foregoing experiments in which the bath was used, but further experiments were carried out in order to make these tests in cats in which the blood pressure was taken from the carotid artery. Fig. 79 is the tracing from a male cat weighing 3.5 K. At A, 0.3 cc.

of brain extract was injected into the saphenous vein, this caused a disturbance of respiration as well as a fall of blood pressure. At B, the same amount was given,after treatment with Norit, but here the fall of blood pressure was much less marked. At C, 0.3 cc. of acetyl choline (1 cc. = 0.006 gramme) was given and this caused a marked fall of blood pressure associated with some disturbance of the respiration. At D, the same dose of acetyl choline, after treatment with Norit, was injected, the fall of blood pressure was as great as in C, and this shows that the Norit does not affect the acetyl choline, and this confirms what was shown in the experiments where the bath was used. In Fig. 80, at A, 0.3 cc. of acetyl choline together with 0.5 mg. of atropine sulphate was injected, and this caused no fall of blood pressure because the atropine had antagonized the action of the acetyl choline. At B, 0.3 cc. of brain extract, after treatment with Norit, together with 0.5 mg. atropine was injected, there was no fall of blood pressure, but Traube Hering Waves developed. This figure shows that the histamine has been adsorbed by the Norit, and the other substance which is presumably acetyl choline has been antagonized by the atropine.

Fig. 81 was from a female cat weighing 2.3 K. A shows the effect of the injection of 0.2 cc. of acetyl choline (1 cc. = 0.006 gramme), the result was a marked fall of blood pressure. The disturbance of the respirations was due to the animal micturating. B shows the effect of the same amount of acetyl choline after treatment with Norit, and it shows that the Norit does not antagonize the acetyl choline.

Fig. 82 was from a female cat weighing 2.4 K. At A, brain extract after treatment with Norit and after the addition of 2 N NaOH was injected into the saphenous vein. There was no fall of blood pressure because the histamine had been removed by the Norit and the alkali which had been added had antagonized the acetyl choline substance. In this case the solution was made up from 1 cc. of brain extract and 1 cc. of 2N NaOH, neutralised and made up to 10 cc. in Tyrode-Bayliss solution. In Fig. 83, at A, 1 cc. of brain extract after treatment with Norit in 10 cc. of Tyrode-Bayliss was injected and this caused a small fall of blood pressure owing to the acetyl choline substance, the

histamine having been removed by the Norit. The disturbance of respiration in this figure was due to the animal moving. This dilution was used to show that the result in the previous figure was not due to the dilution used. In Fig. 84, at A, 1 cc. of brain extract, after treatment with Norit, to-: gether with the animal's own whole blood caused a fall of blood pressure. This shows that the esterase which is supposed to be present in the blood did not completely neutralise the acetyl choline sub-: stance. In Fig. 85, A shows the effect of the intravenous injection of 0.3 mg. of eserine. This had no effect on the blood pressure, and this was the result expected. In Fig. 86, the animal had pre-: viously been given intravenous injection of eserine. At A, 0.3 cc. of brain extract, after treatment with Norit, was injected and this caused a marked fall of blood pressure and as the histamine had been previous-: ly removed by the Norit, this fall of blood pressure was due to acetyl choline, and the more marked fall in this case was because the eserine prolongs the action of the acetyl choline. In Fig. 87, at A, one drop of a solution of 0.01 gramme of acetyl cho-

:line in 3 cc. of the animal's own blood was injected. This caused a marked fall of blood pressure and at B, artificial respiration was given. This figure shows that the eserine prolongs the action of acetyl choline, and also proves that the esterase in the blood does not antagonize the acetyl choline.

This acetyl choline substance which is present in the brain extract gave all the tests for acetyl choline which I have mentioned, except that in which blood was used. This last group of experiments confirms the findings in the previous groups that there are at least two depressor substances present in the brain, one which is either histamine or a histamine-like substance and the other which is either acetyl choline or an acetyl choline-like substance.

CONCLUSIONS.

1. When trauma, apart from severe haemorrhage, is applied to the brain, and when the intracranial pressure is raised, there is little effect on the blood pressure, provided that the intra-:cranial pressure remains below the level of the blood pressure.
2. When the intracranial pressure approaches the level of the blood pressure, the latter shows a small rise which it tends to maintain, if the intracranial tension does not continue to rise. This rise of the blood pressure is due to an attempt on the part of the vaso-motor centre to overcome the anaemia of the brain.
3. When the intracranial tension continues to rise and reaches a higher level than that of the blood pressure, the vaso-motor centre is no longer able to overcome the anaemia of the brain, and the blood pressure falls sharply.
4. If the high intracranial tension be maintained, the animal will die unless artificial respira-:tion is given.

5. The respiratory centre is the first of the vital centres in the medulla to be involved, and fai-:lure of the respiratory centre is the cause of death.

6. Trauma, applied locally to one part of the cerebral hemisphere, if severe, rapidly spreads throughout the brain and involves the vital cen-:tres in the medulla.

7. The experiments in which the hypothalamus was divided indicate that the accessory sympathetic centres in the hypothalamus do not influence the effects of trauma to the brain.

8. When the stellate ganglia are removed and when the vagi are also divided, there is no difference in the results of trauma or increased intracranial pressure. This means presumably that the heart itself does not play an important part in the pro-:duction of the results of trauma.

9. There are at least two depressor substances pre-:sent in the brain. These are histamine or a histamine-like substance and acetyl choline or an acetyl choline-like substance.

10. Considering the universal distribution of histamine and the ease with which it is liberated, and the markedly depressant effect of very minute doses of acetyl choline, it is possible to assume, that, in trauma to the brain, small amounts of these substances may be liberated into the blood stream. In my experiments the acetyl choline-like substance was not destroyed by the esterase in the blood.

11. In cases of trauma to the brain it is possible that there are two factors operating, firstly a factor due to the increased intracranial pressure involving the medullary centres, and secondly, a factor due to the liberation of the depressant substances, which are present in the brain, into the blood stream.

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UNIVERSITY OF GLASGOW.

Ch.M. Thesis.

AN EXPERIMENTAL INVESTIGATION OF THE EFFECTS OF TRAUMA TO THE CENTRAL NERVOUS SYSTEM

by

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M.C., M.A.,Oxon., M.B., Ch.B.,Glasg.

VOLUME II.

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The drawing in Fig. 1 was made by A. R. Smellie, the drawings in Figs. 2 and 69 were made by J. R. Bell.

All the other illustrations were taken from the records of the actual experiments. The original tracings from which the illustrations were made are available for examination.

The blood pressure (B.P.) scale is shown on the right hand side, and where the intracranial pressure (I.C.P.) is recorded it is shown on the left hand side.

Where both the blood pressure and the intracranial pressure are recorded, it was found impossible, in most cases, owing to technical difficulties, to place them on the same zero line.

The record of the respiratory movements, when shown, forms the uppermost tracing in the illustrations.

Fig. 1.

The modified Sherrington stethograph which was used in experiments.

Fig. 2.

Apparatus for recording the intracranial pressure.

1. Adjustable stand for manometer.
2. Manometer with writing style.
3. Pressure bottle.
4. Pressure bulb with button release.
5. Brass cannula in circuit.
6. Screw clamp.

A. Actual size of the brass cannula showing the threaded end which is screwed into the trephine opening.

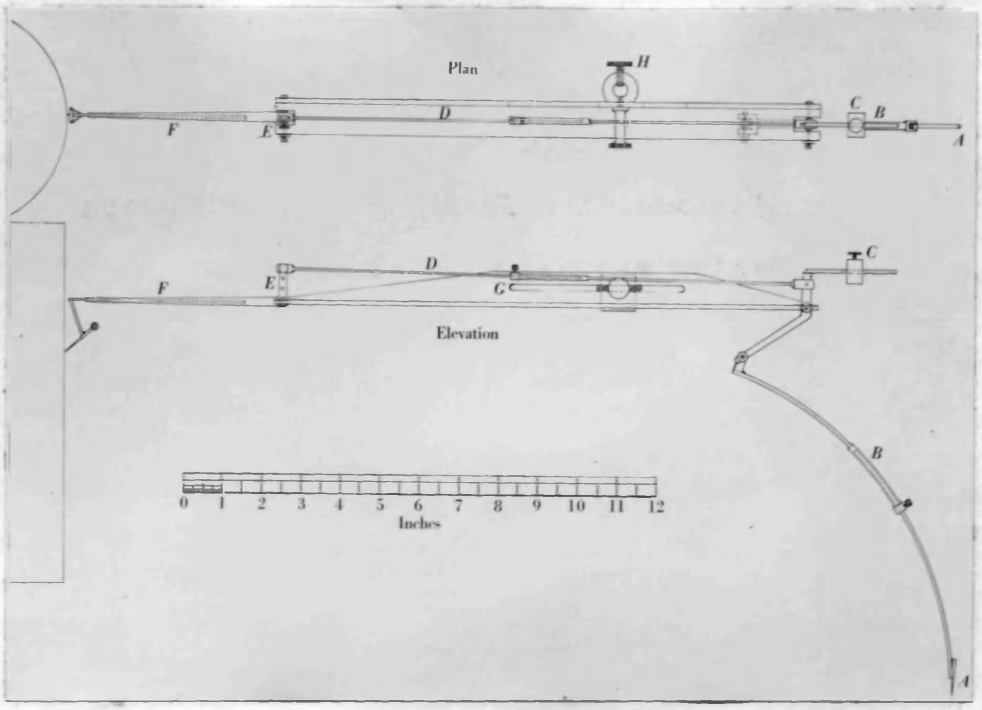


FIG. 1.

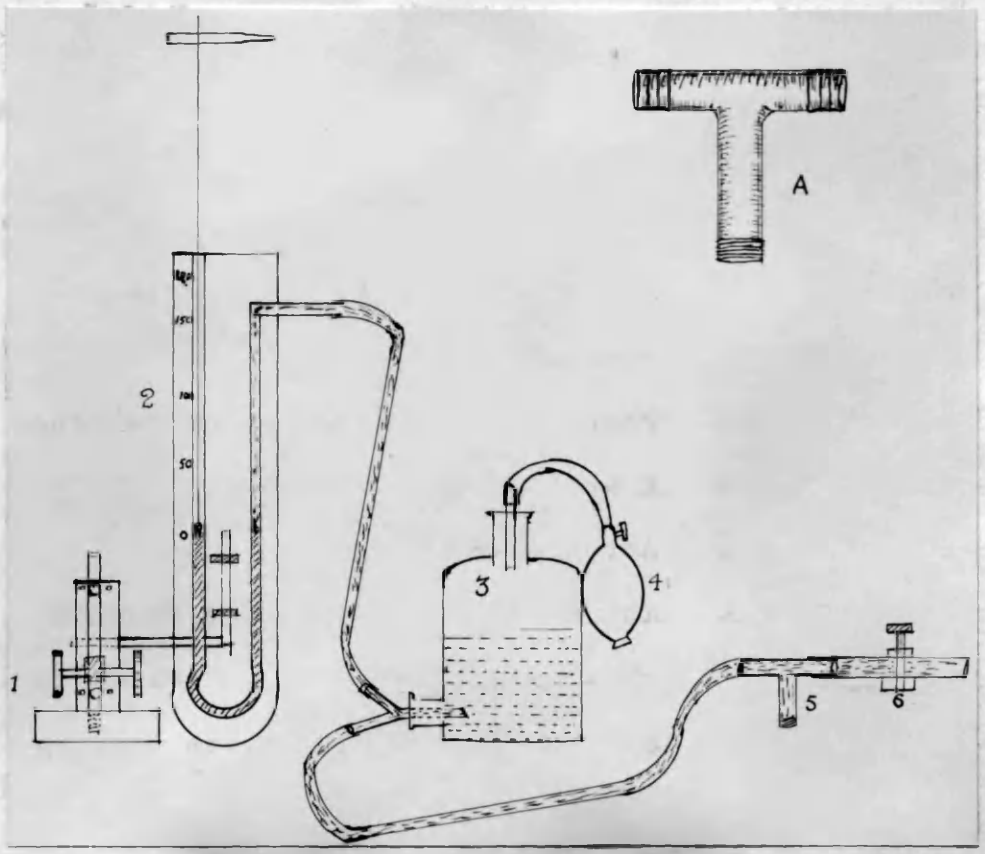


FIG. 2.

Fig. 3.

Blood pressure tracing from cat weighing 3.7 K.

A. Pressure to brain through trephine opening.

B. Pressure removed.

Fig. 4.

From the same animal as Fig. 3.

A. Pressure on brain.

B. Pressure removed.

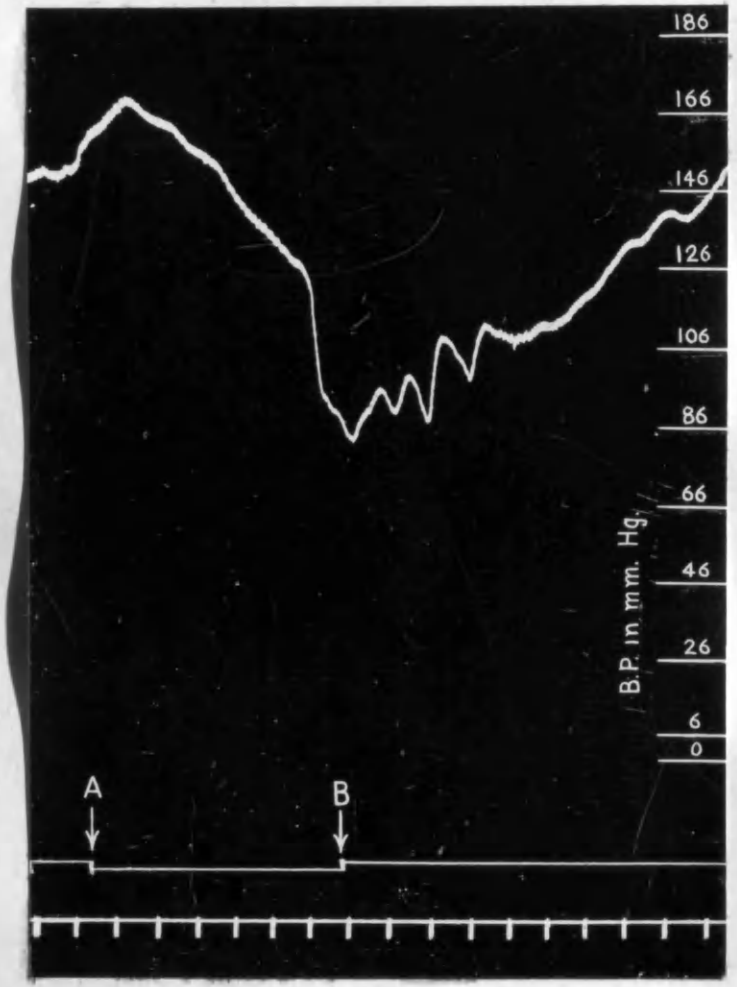

186
166
146
126
106
86
66
46
26
6
0
B.P. in mm. Hg.
A
B

FIG. 4.

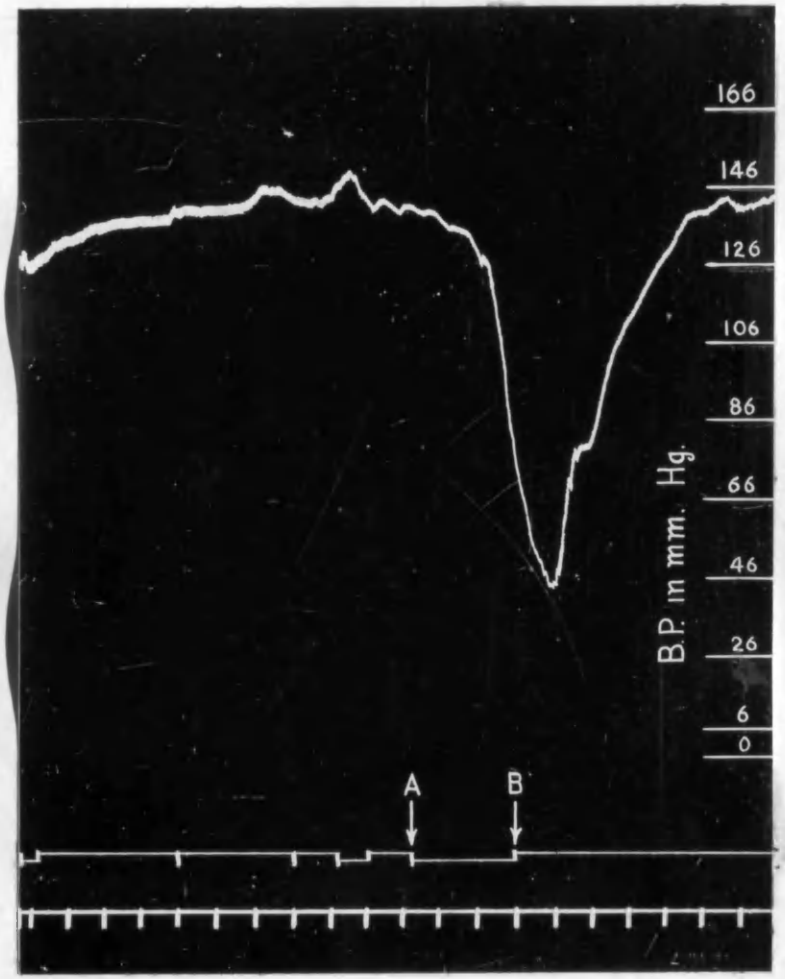

166
146
126
106
86
66
46
26
6
0
B.P. in mm. Hg.
A
B

FIG. 3.

Fig. 5.

From the same animal.

A. Pressure on brain.

B. Animal stopped breathing, artificial respiration.

Fig. 6.

Blood pressure tracing from cat weighing 2.4 K.

A. Pressure on brain.

B. Artificial respiration.

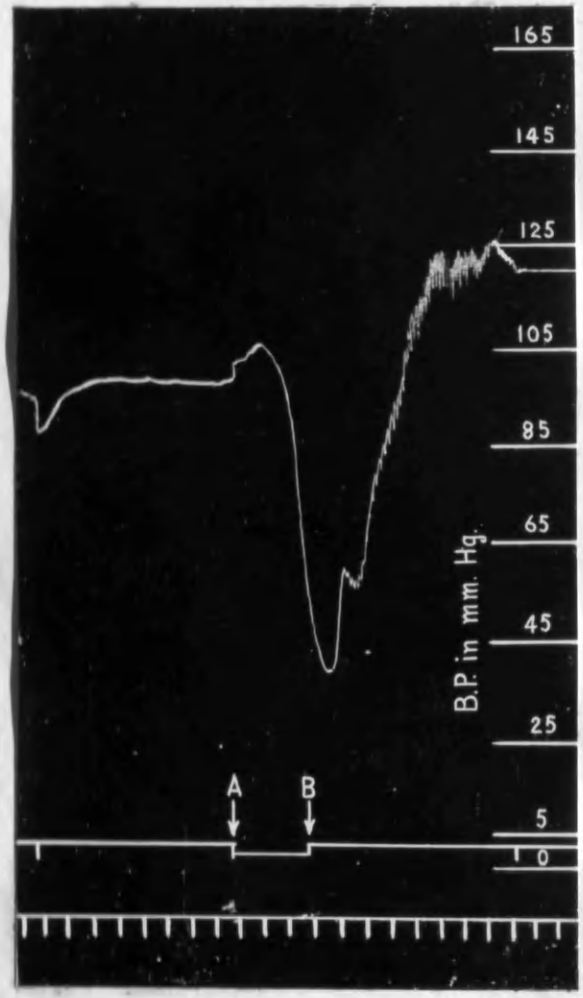

165
145
125
105
85
65
45
25
5
0
B.P. in mm. Hg.
A
B

Fig. 6.

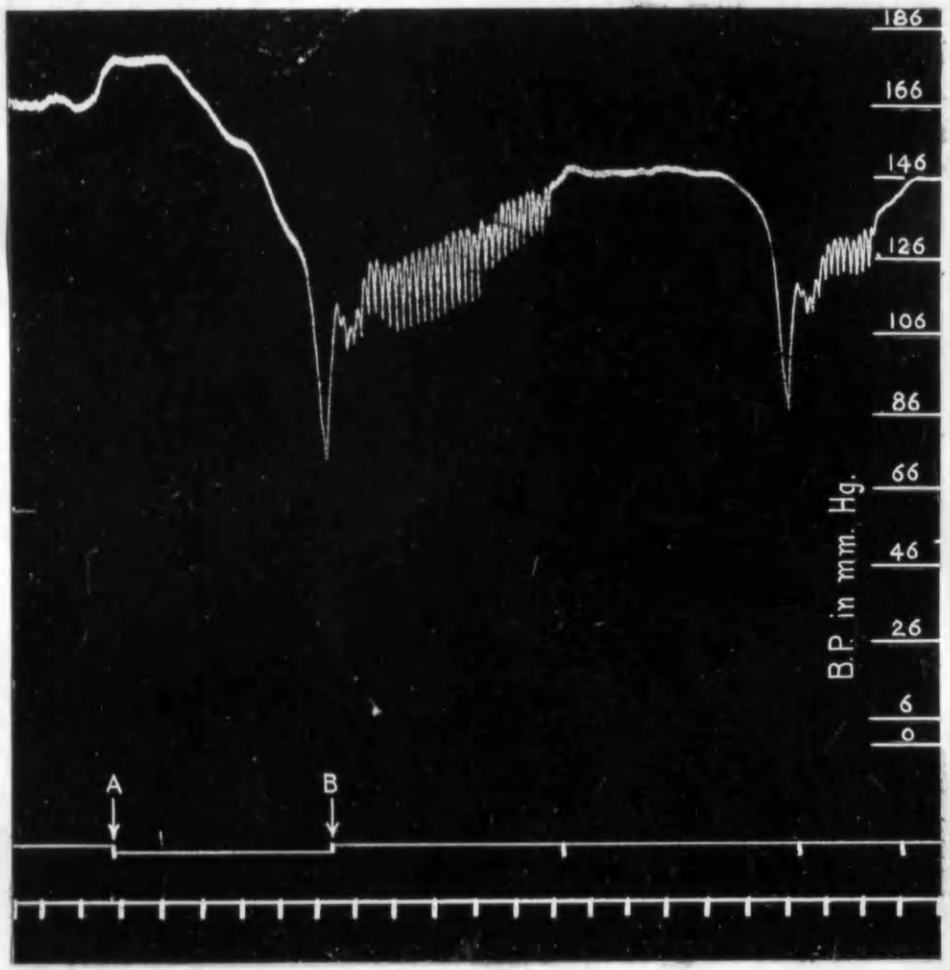

186
166
146
126
106
86
66
46
26
6
0
B.P. in mm. Hg.
A
B

Fig. 5.

Fig. 7.

Record from cat weighing 3.1 K.

Upper tracing shows respiratory movements.

Lower tracing blood pressure.

A. Pressure applied through the intact dura mater.

B. Artificial respiration.

C. Artificial respiration stopped.

Fig. 8.

From the same animal.

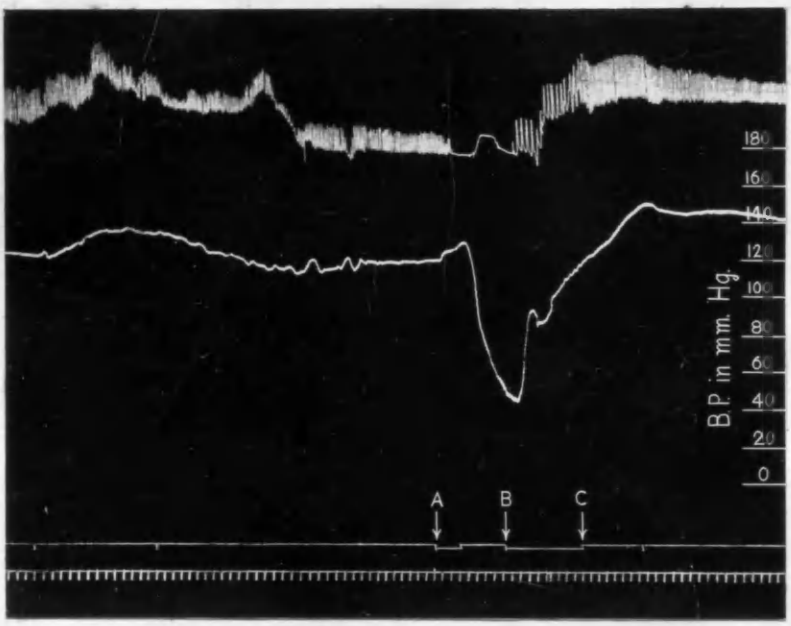
A. Pressure on brain.

B. Artificial respiration.

C. Artificial respiration stopped.

D. Right vagus divided.

E. Left vagus divided.


180
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140
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100
80
60
40
20
0
B.P. in mm. Hg.
A
B
C

FIG. 7.

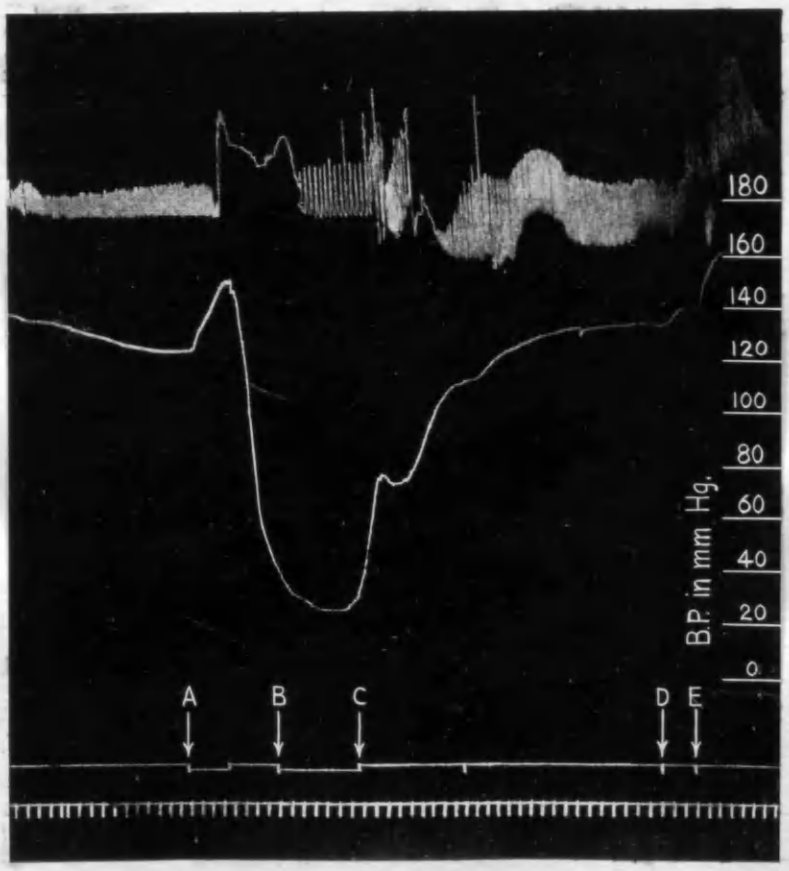

180
160
140
120
100
80
60
40
20
0
B.P. in mm Hg.
A
B
C
D
E

FIG. 8.

Fig. 9.

Record from cat weighing 3 K.

A. Small portion of brain removed, and pressure applied.

B. Pressure removed.

C. Artificial respiration.

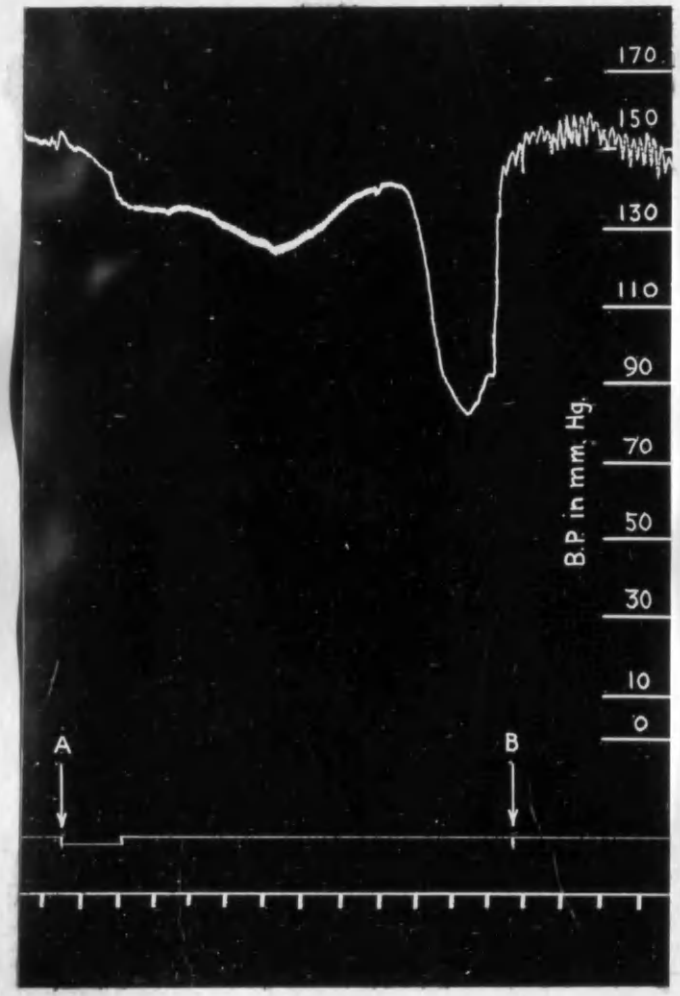
D. Artificial respiration stopped.

Fig. 10.

Record from cat weighing 2.4 K.

A. Instrument introduced through trephine hole and stirred round in the brain.

B. Artificial respiration.


170
150
130
110
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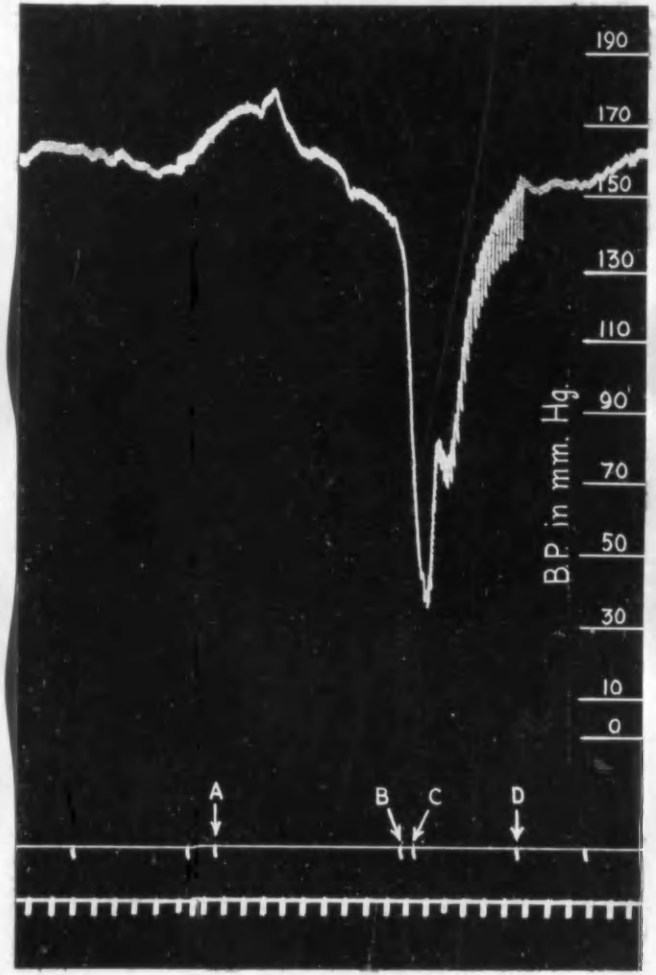
70
50
30
10
0
B.P. in mm. Hg.
A
B

Fig. 10.


190
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0
B.P. in mm. Hg.
A
B
C
D

Fig. 9.

Fig. 11.

Record from a cat weighing 3.2 K., of the respiratory movements, blood pressure and the intracranial pressure.

A. Pressure in the intracranial pressure apparatus raised.

B. This pressure suddenly com-:municated to the brain.

C. Intracranial pressure sud-:denly lowered to zero.

D, E and F show the same procedure.

Fig. 12.

Record from a cat weighing 2 K., of the respiratory movements, blood pressure and intracranial pressure.

A. Pressure in apparatus raised.

B. This pressure suddenly com-:municated to the brain.

C. Intracranial pressure suddenly lowered to zero.

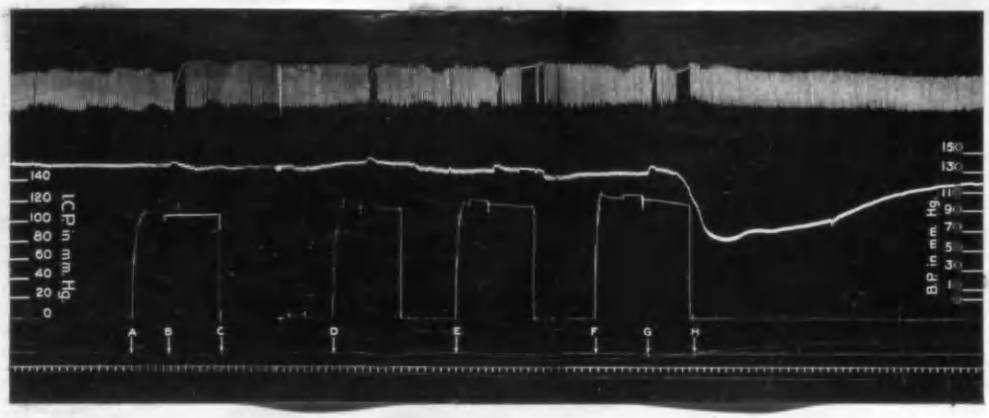

I.C.P. in mm. Hg.
140
120
100
80
60
40
20
0
B.P. in mm. Hg.
150
130
A
B
C
D
E
F
G
H

FIG. 11.

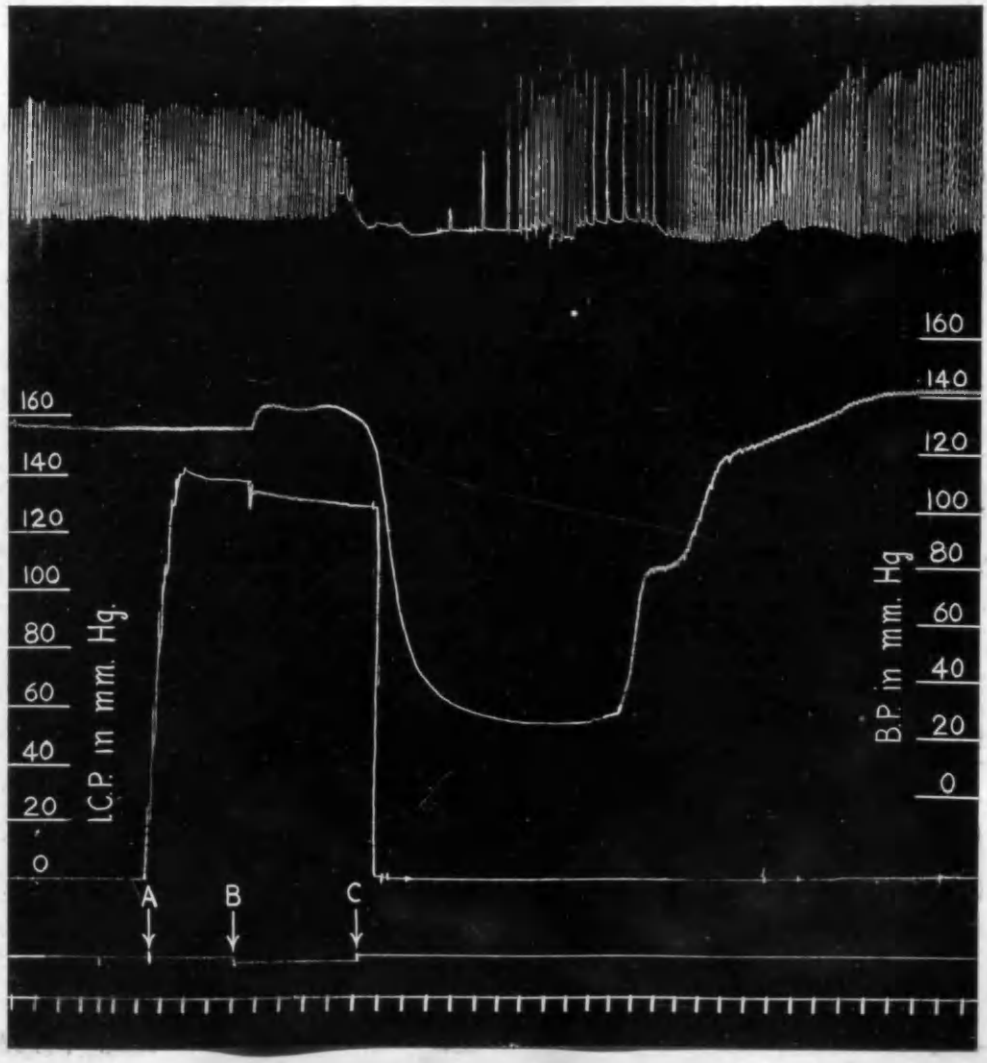

I.C.P. in mm. Hg.
160
140
120
100
80
60
40
20
0
B.P. in mm. Hg
160
140
120
100
80
60
40
20
0
A
B
C

FIG. 12.

Fig. 13.

Record from a cat weighing 3.4 K., of the respiratory movements, blood pressure and intracranial pressure.

A. Pressure in apparatus raised.

B. This pressure suddenly communicated to the brain.

C. Intracranial pressure suddenly lowered to zero.

D. Artificial respiration.

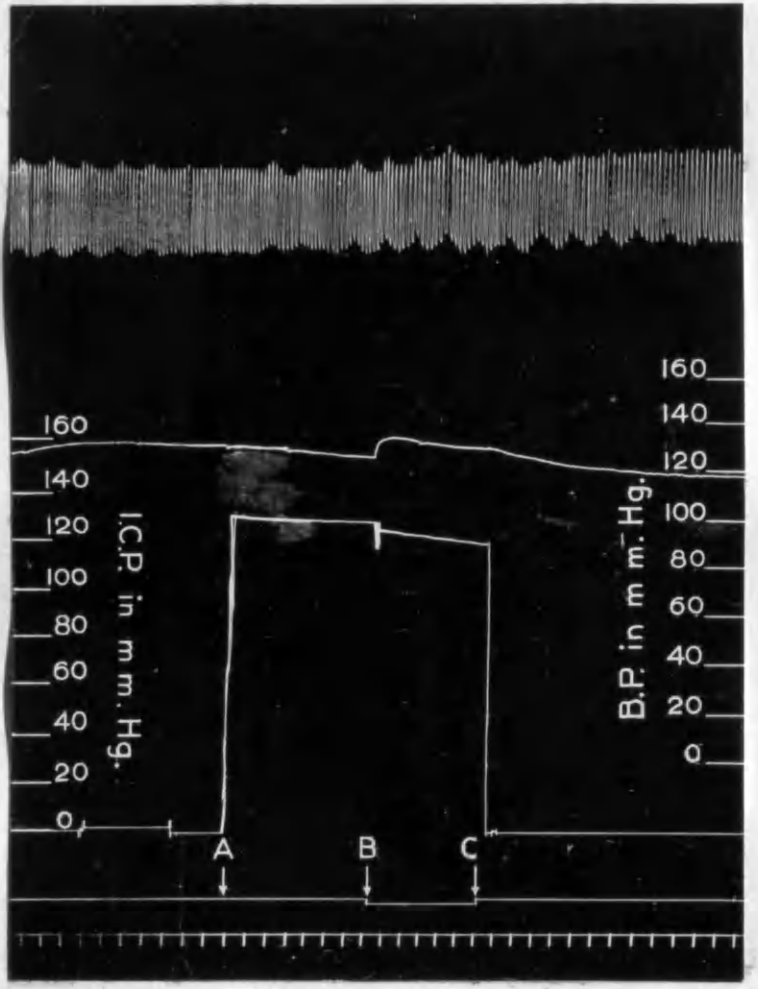
Fig. 14.

Record from a cat weighing 2 K., of the respiratory movements, blood pressure, and intracranial pressure.

A. Pressure in the apparatus raised.

B. This pressure suddenly communicated to the brain.

C. Intracranial pressure suddenly lowered to zero.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140
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80
60
40
20
0
I.C.P. in m m. Hg.
160
140
120
100
80
60
40
20
0
B.P. in m m. Hg.
A
B
C

FIG. 14.

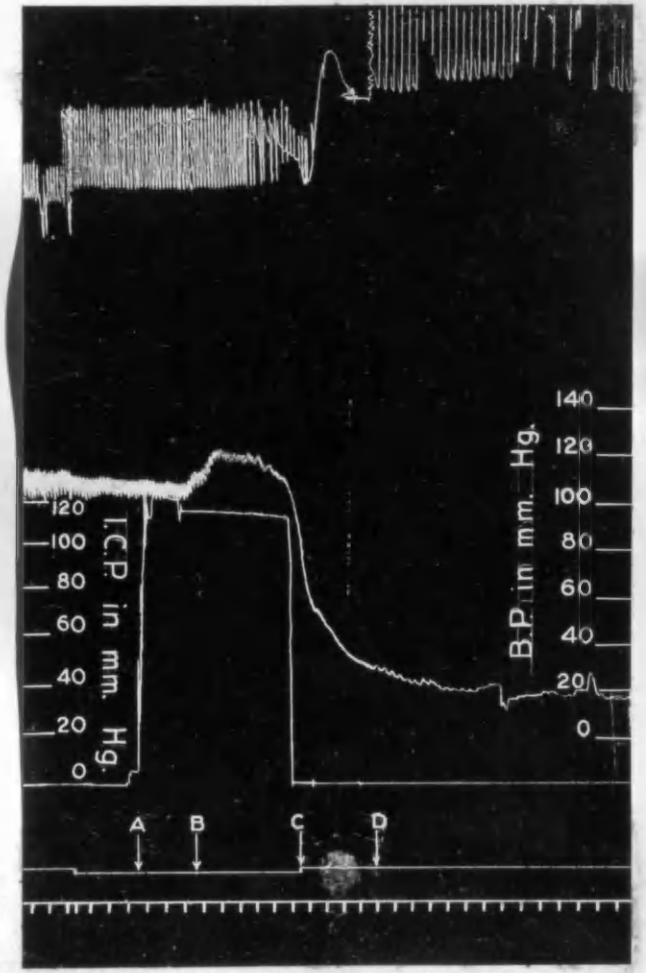

120
100
80
60
40
20
0
I.C.P. in mm. Hg.
140
120
100
80
60
40
20
0
B.P. in mm. Hg.
A
B
C
D

FIG. 13.

Fig. 15.

Record from the same animal as Fig. 14.

A. Pressure in apparatus raised.

B. This pressure suddenly communicated to the brain.

C. Intracranial pressure sud-:denly lowered to zero.

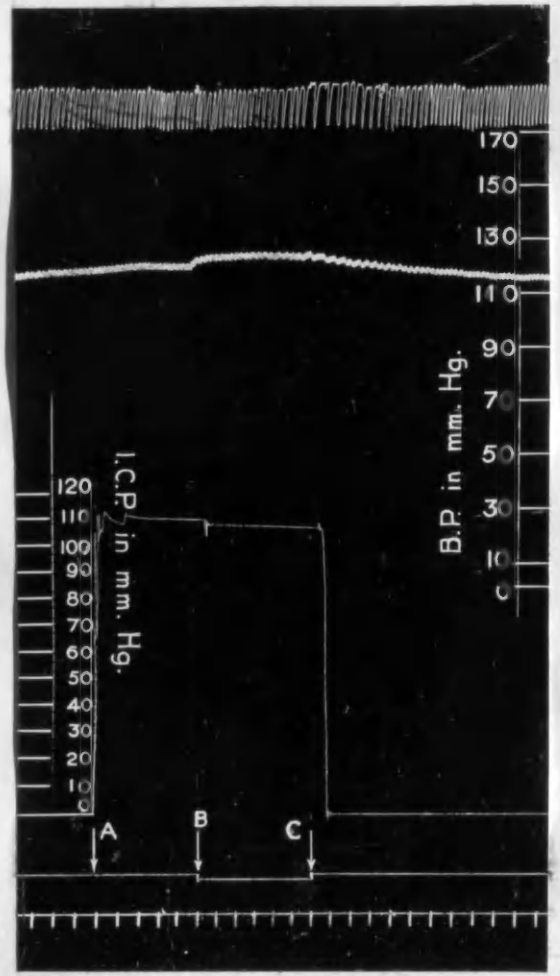
Fig. 16.

Record from a cat weighing 2.2 K., of the respiratory movements, blood pressure and intracranial pressure.

A. Pressure in apparatus raised.

B. This pressure suddenly communicated to the brain.

C. Intracranial pressure sud-:denly lowered to zero.


170
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70
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30
10
B.P. in mm. Hg.
120
110
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90
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70
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50
40
30
20
10
I.C.P. in mm. Hg.
A
B
C

FIG. 16.

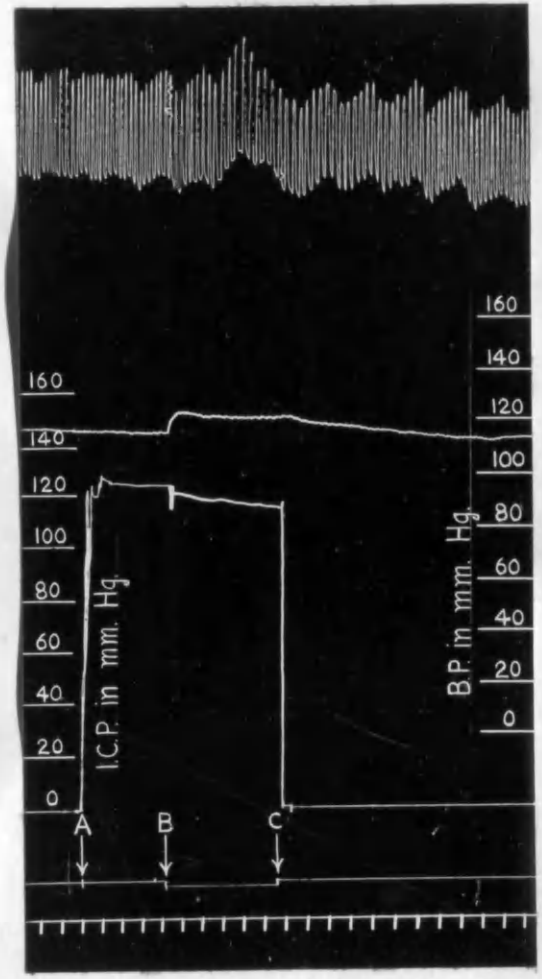

160
140
120
100
80
60
40
20
0
I.C.P. in mm. Hg.
160
140
120
100
80
60
40
20
0
B.P. in mm. Hg.
A
B
C

FIG. 15.

Fig. 17.

Record from a cat weighing 2.5 K., of the respiratory movement, blood pressure and intracranial pressure. Shows the effect of gradually rais-:ing the intracranial pressure to a level higher than that of the blood pressure, and then gradually lower-:ing it to a level below that of the blood pressure.

Fig. 18.

Record from same animal as Fig.17. Shows the effect of gradually raising the intracranial pressure, and of lowering it suddenly to zero.

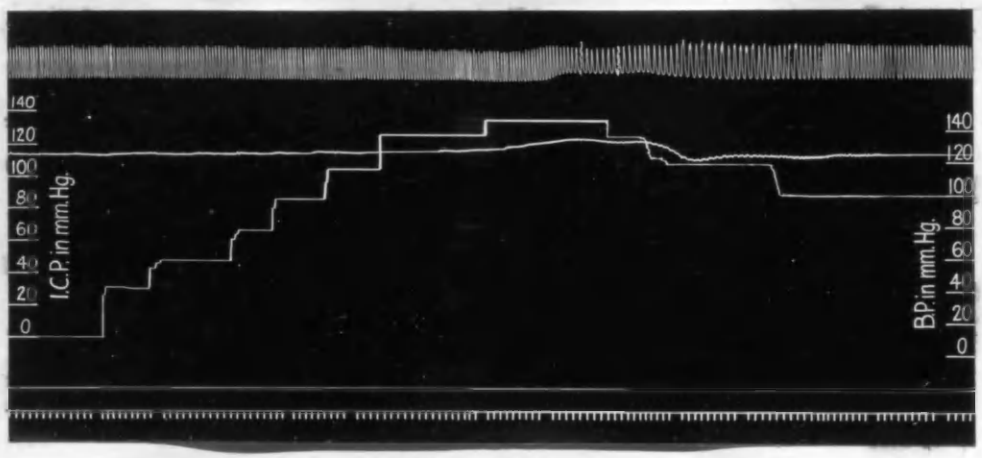

140
120
100
80
60
40
20
0
I.C.P. in mm.Hg.
140
120
100
80
60
40
20
0
B.P. in mm.Hg.

FIG. 17.

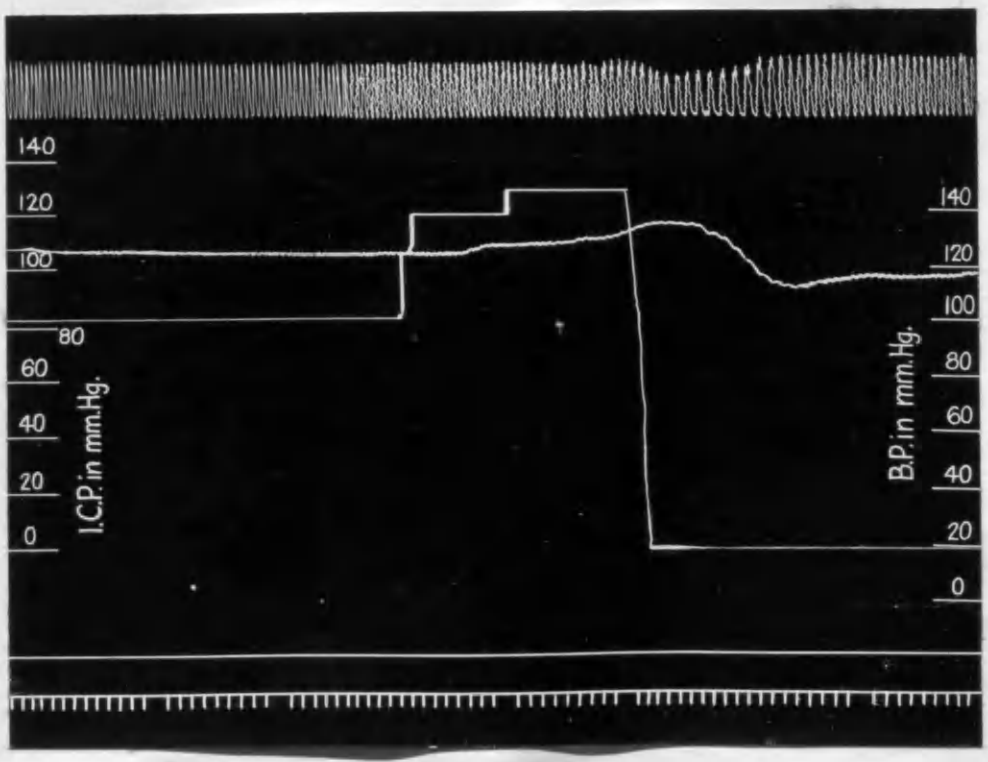

140
120
100
80
60
40
20
0
I.C.P. in mm.Hg.
140
120
100
80
60
40
20
0
B.P. in mm.Hg.

FIG. 18.

Fig. 19.

Record from same animal as previous one. The intracranial pressure was gradually raised and gradually lowered.

A. Artificial respiration.

Fig. 20.

Record from a cat weighing 2.3 K., of the respiratory movements, blood pressure and intracranial pressure. The intracranial pressure was gradually raised, then gradually lowered to zero.

A. Artificial respiration.

B. Artificial respiration stopped.

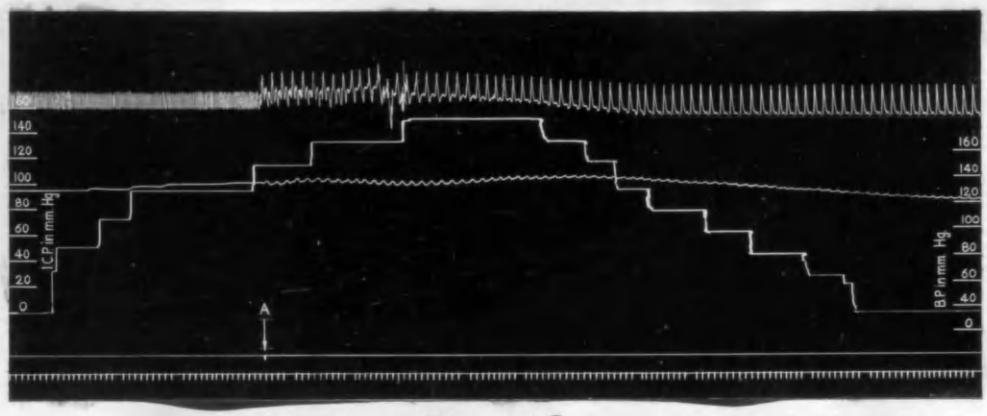

160
140
120
100
80
60
40
20
0
I.C.P in mm Hg
160
140
120
100
80
60
40
0
B.P in mm Hg
A

FIG. 19.

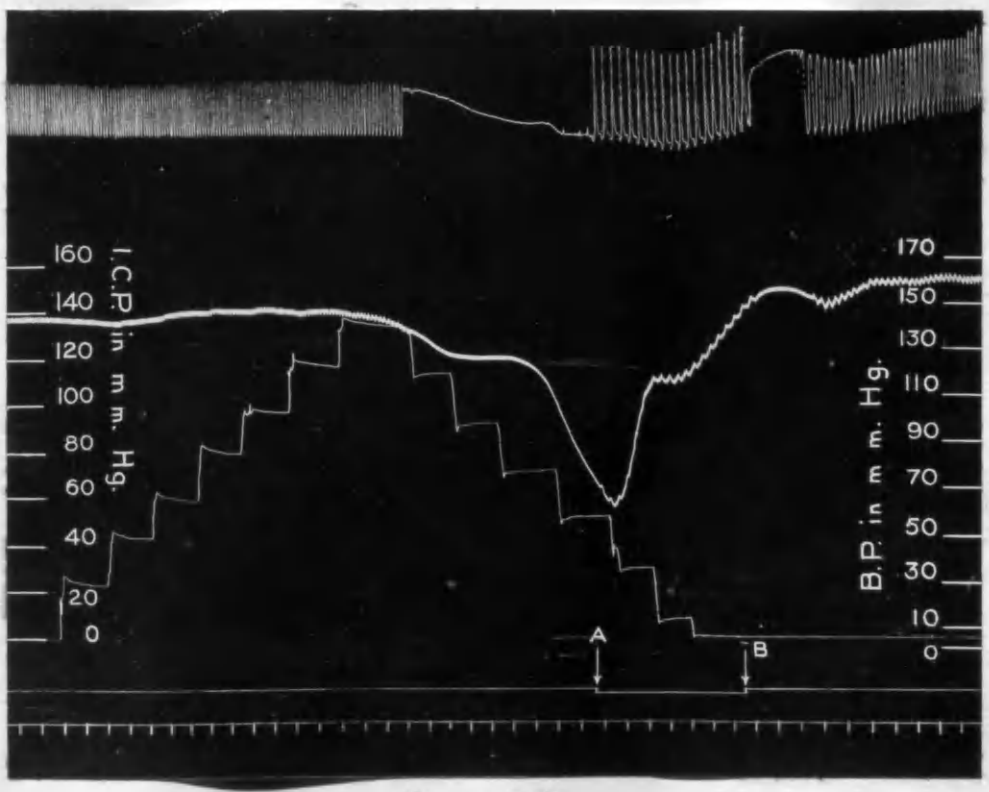

160
140
120
100
80
60
40
20
0
I.C.P in m m. Hg.
170
150
130
110
90
70
50
30
10
0
B.P. in m m. Hg.
A
B

FIG. 20.

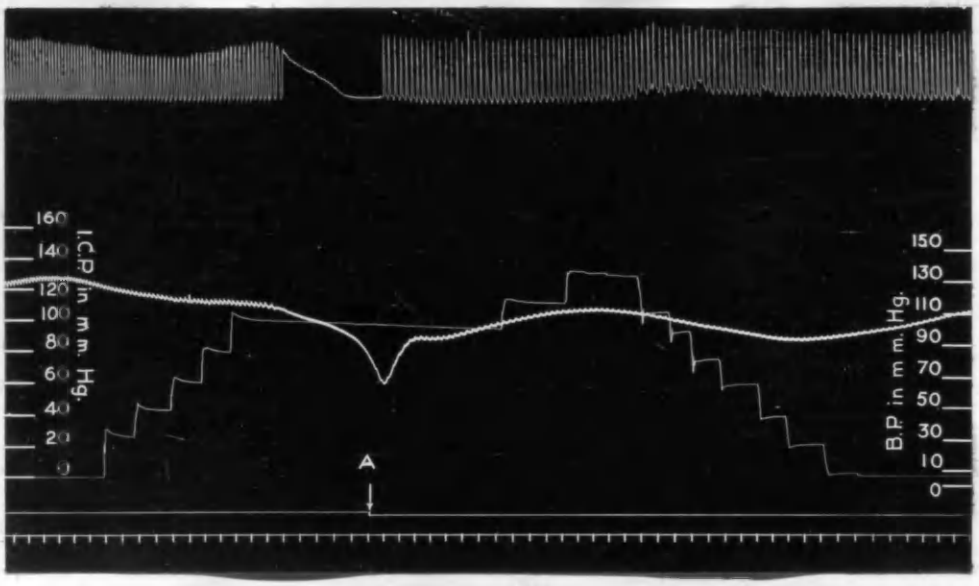
Fig. 21.

Record from same animal as Fig. 20.
Shows much the same procedure.

A. Artificial respiration.

Fig. 22.

Shows the extent to which intra-
:cranial pressure can be raised,
when artificial respiration is
maintained.


I.C.P. in m m. Hg.
160
140
120
100
80
60
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A
B.P. in m m. Hg.
150
130
110
90
70
50
30
10
0

FIG. 21.

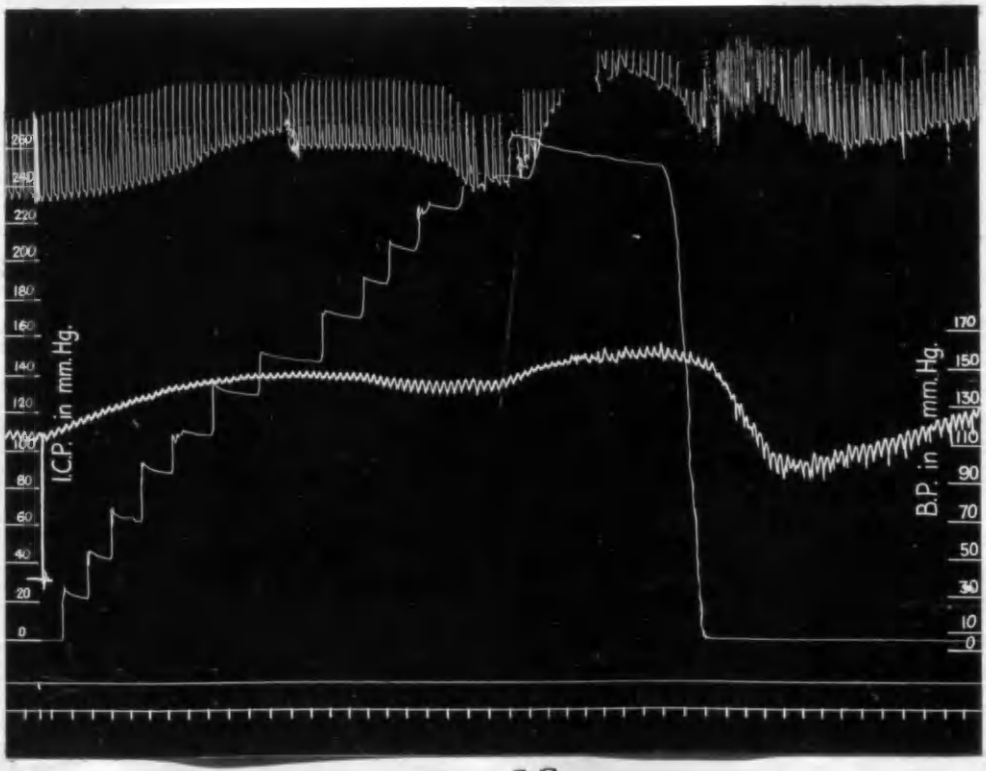

I.C.P. in mm.Hg.
260
240
220
200
180
160
140
120
100
80
60
40
20
0
B.P. in mm.Hg.
170
150
130
110
90
70
50
30
10
0

FIG. 22.

Fig. 23.

Record from a cat weighing 3.4 K. Shows the effect on the blood pressure during the operation of trephining the basi-sphenoid.

Fig. 24.

A record from the same animal as Fig. 23.

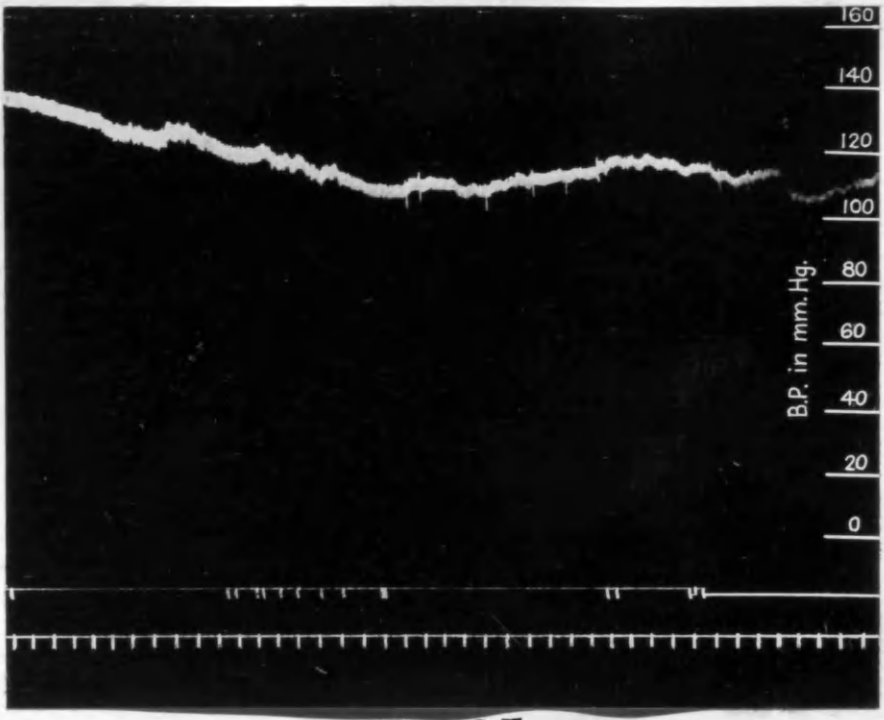
A. Hypothalamus divided. Between B and C, the skull was trephined.

D. Pressure on the brain.

E. Pressure removed.

F. Pressure on the brain.

G. Pressure removed.


160
140
120
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80
60
40
20
0
B.P. in mm. Hg.

FIG. 23.

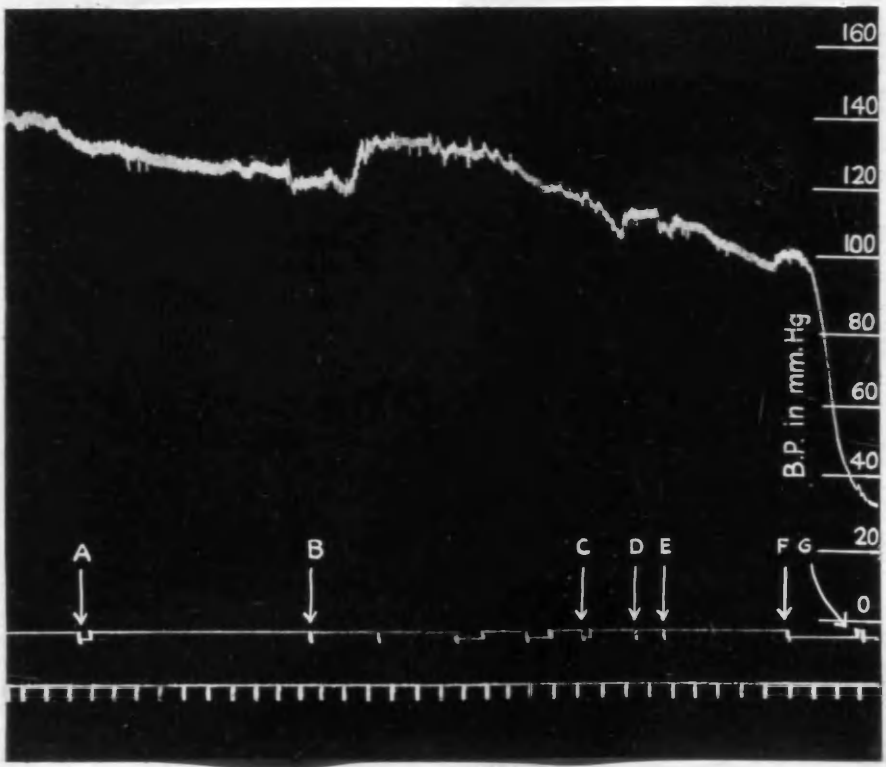
160
140
120
100
80
60
40
20
0
B.P. in mm. Hg
A
B
C
D
E
F
G

FIG. 24.

Fig. 25.

Record from a cat weighing 3.2 K.

A. Hypothalamus divided while animal was getting artificial respiration.

Fig. 26.

Record from a cat weighing 3 K.

A. Hypothalamus divided.

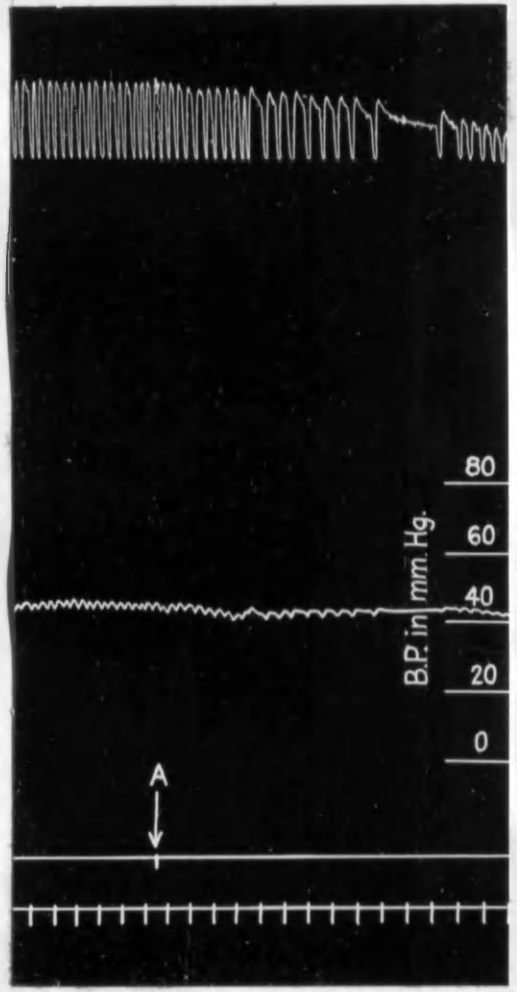

FIG. 26.

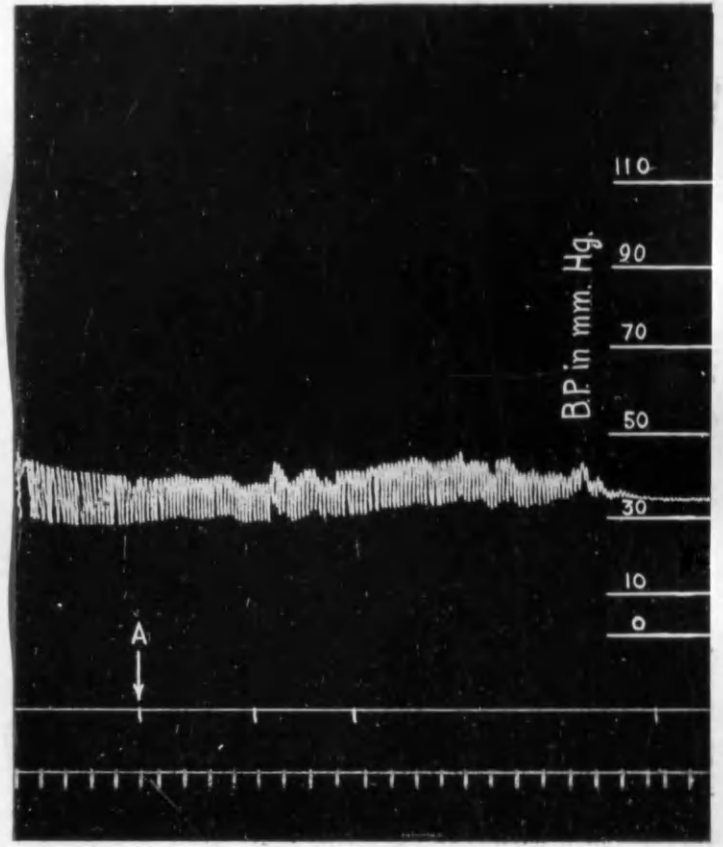

FIG. 25.

Fig. 27.

Record from a cat weighing 3.2 K.

A. Hypothalamus divided.

Fig. 28.

Record from the same animal as Fig.27. After division of the hypothalamus.

A. Pressure on the brain.

B. Pressure removed.

C. Artificial respiration

D. This procedure repeated.

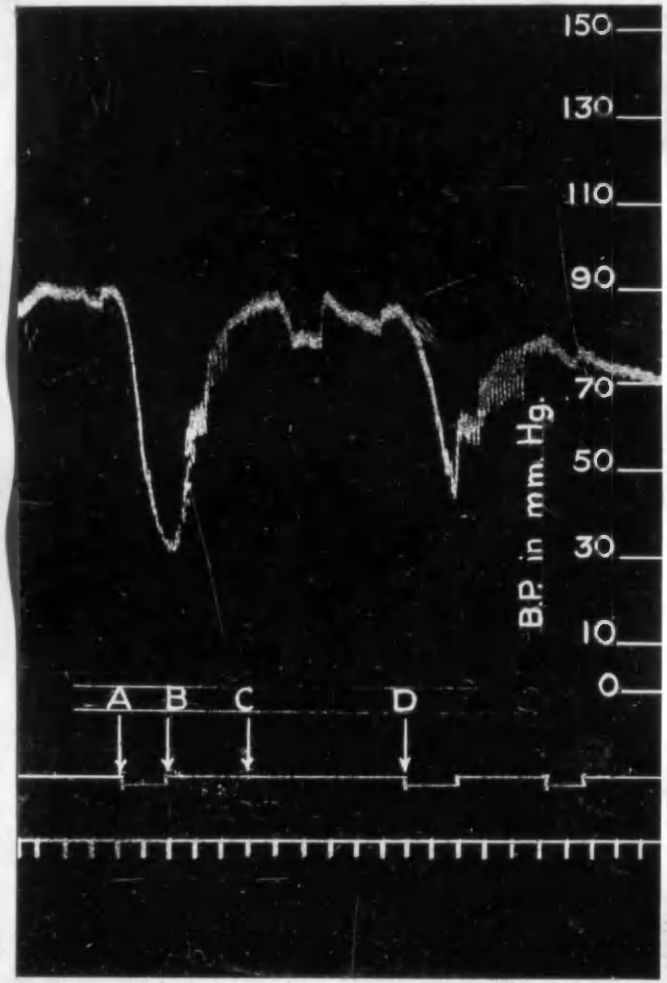
150
130
110
90
70
50
30
10
0
B.P. in mm. Hg.
A B C D

Fig. 28.


150
130
110
90
70
50
30
10
0
B.P. in mm. Hg.
A

Fig. 27.

Fig. 29.

Hypothalamus was divided previously.

A. Artificial respiration stopped.

B. Vagi divided.

C. Pressure on brain.

D. Pressure removed.

E. Artificial respiration.

F. Artificial respiration stopped.

G. Pressure on brain.

Fig. 30.

Hypothalamus was divided previously.

Artificial respiration continuous.

A. Pressure on brain.

B. Pressure removed.

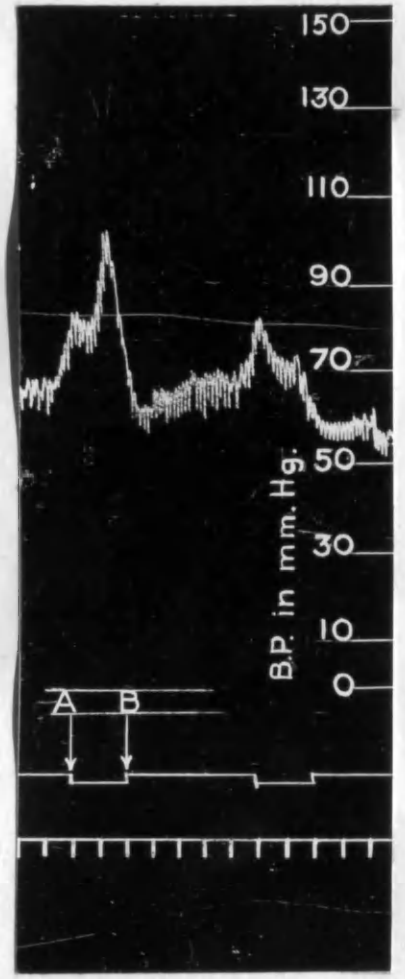
150
130
110
90
70
50
30
10
0
B.P. in mm. Hg.
A
B

Fig. 30.

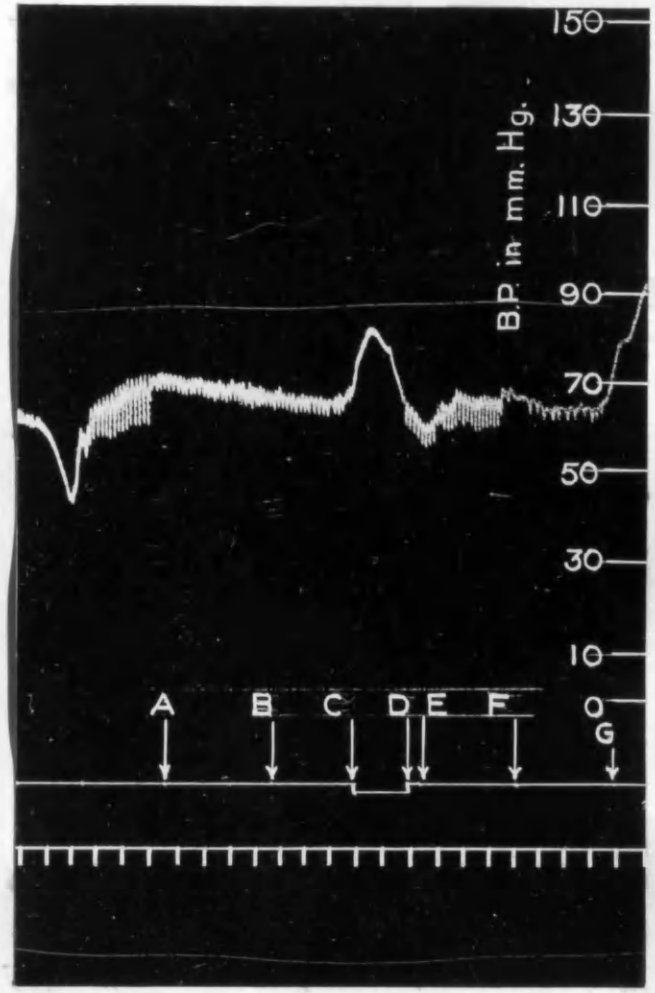
150
130
110
90
70
50
30
10
0
B.P. in mm. Hg.
A
B
C
D
E
F
G

Fig. 29.

Fig. 31.

Photograph of a cat's brain (enlarged).

A. Shows where the hypothalamus was divided.

B. Shows where trauma was ap-
:plied to the brain through
a trephine opening.

Fig. 32.

Photograph of a cat's brain (enlarged). The arrow indicates the position of the electrodes during stimulation of the hypothalamus.

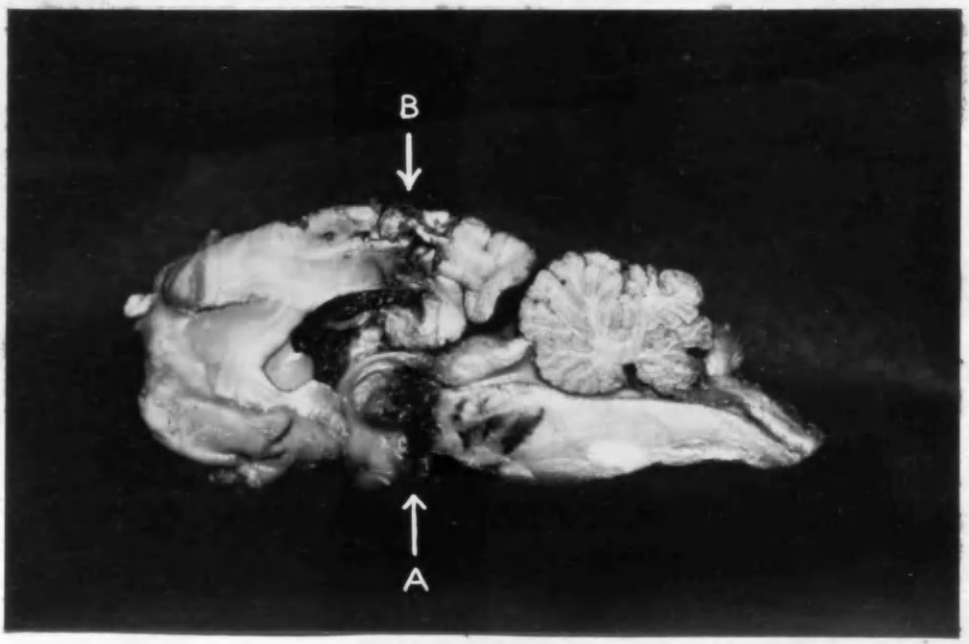

FIG. 31.

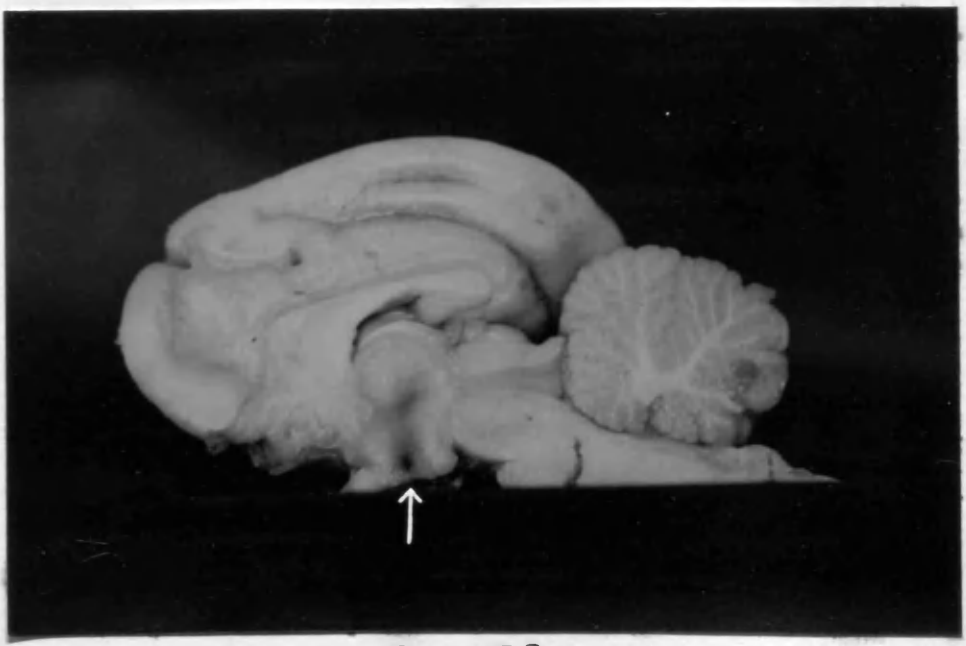

FIG. 32.

Fig. 33.

Record from a cat weighing 3.2 K.

A. Hypothalamus stimulated with coil at 20 cm.

B. " " " " " 10 cm.

C. " " " " " 10 cm.

D. " " " " " 10 cm.

Fig. 34.

Record from a cat weighing 2.2 K.

A. Hypothalamus stimulated with coil at 10 cm.

B. " " " " " 5 cm.

C. " " " " " 5 cm.

D. " " " " " 10 cm.

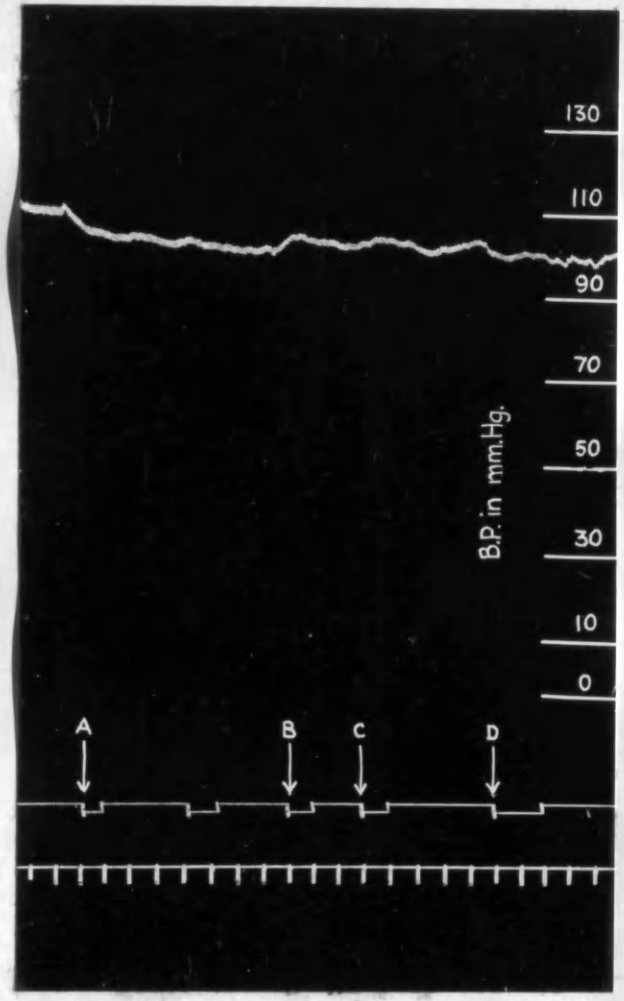
130
110
90
70
50
30
10
0
B.P. in mm.Hg.
A
B
C
D

FIG. 34.

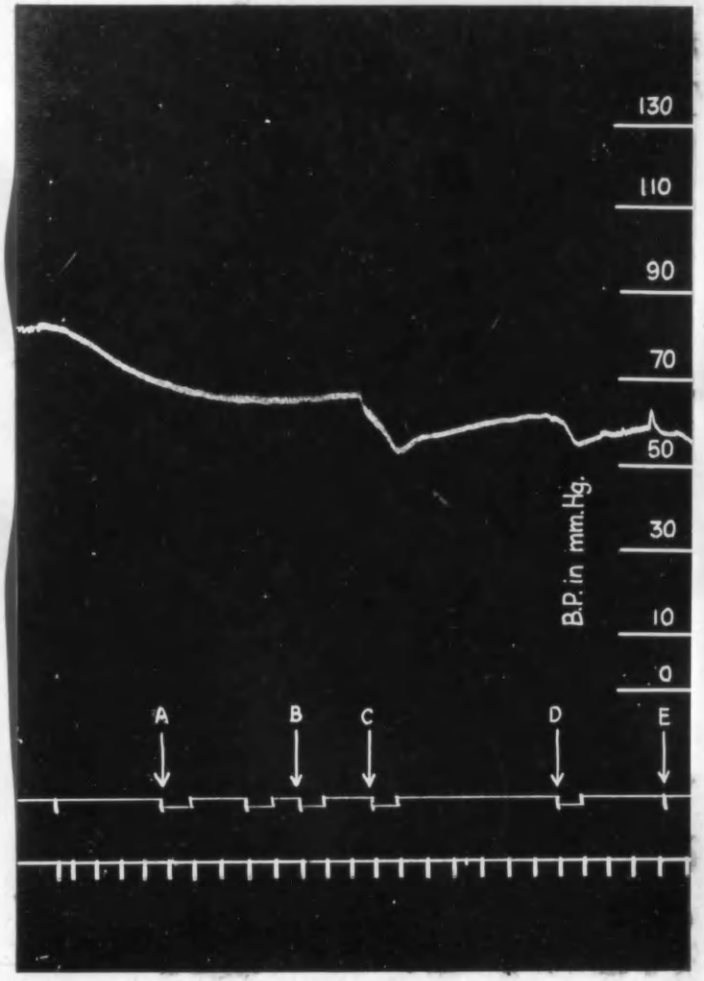
130
110
90
70
50
30
10
0
B.P. in mm.Hg.
A
B
C
D
E

FIG. 33.

Fig. 35.

Record from a cat weighing 3.5 K. Both stellate ganglia were previously removed.

A. Pressure on brain.

B. Pressure off.

C. Artificial respiration.

D. Pressure on brain.

E. Pressure off.

Fig. 36.

Shows a later stage in the same experiment as Fig. 35.

A. Pressure on brain.

B. Pressure off.

C. Vagi divided.

D. Pressure on brain.

E. Pressure off.

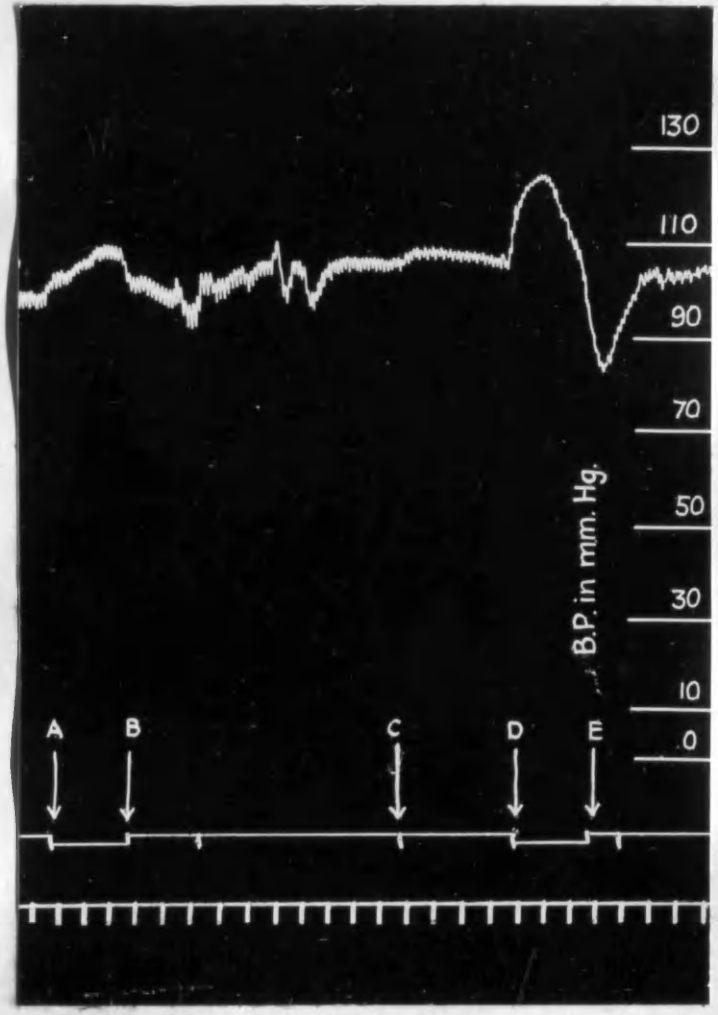
130
110
90
70
50
30
10
0
B.P. in mm. Hg.
A
B
C
D
E

Fig. 36.

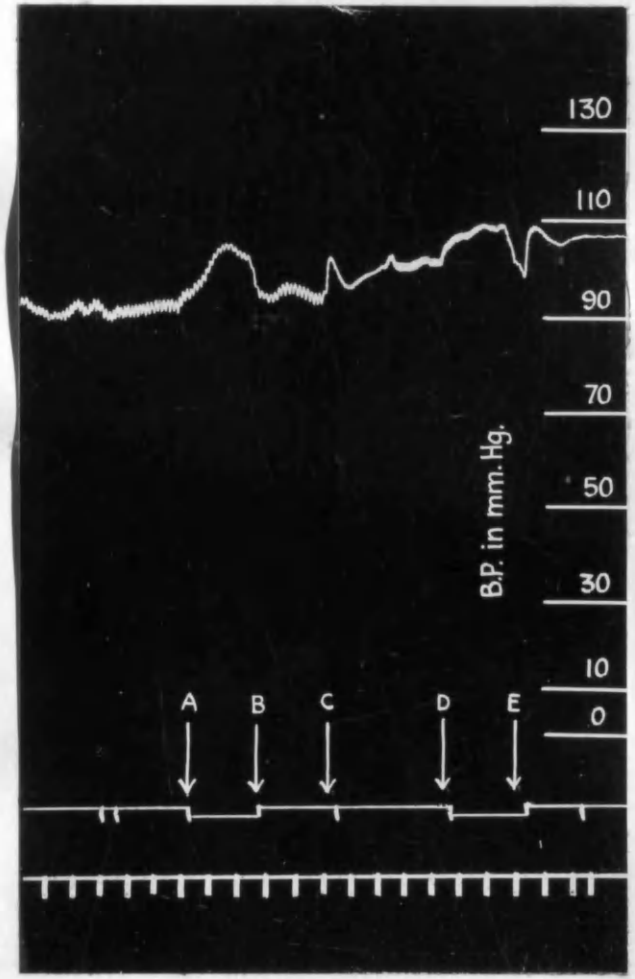
130
110
90
70
50
30
10
0
B.P. in mm. Hg.
A
B
C
D
E

Fig. 35.

Fig. 37.

Record from a cat weighing 3 K.

Both stellate ganglia removed.

Artificial respiration continuous.

A. Pressure on brain.

B. Pressure off.

C. Pressure on brain.

D. Pressure off.

Fig. 38.

Record from the same cat as Fig. 37.

A. Pressure on brain.

B. Pressure off.

C. Vagi divided.

D. Pressure on brain.

E. Pressure off.

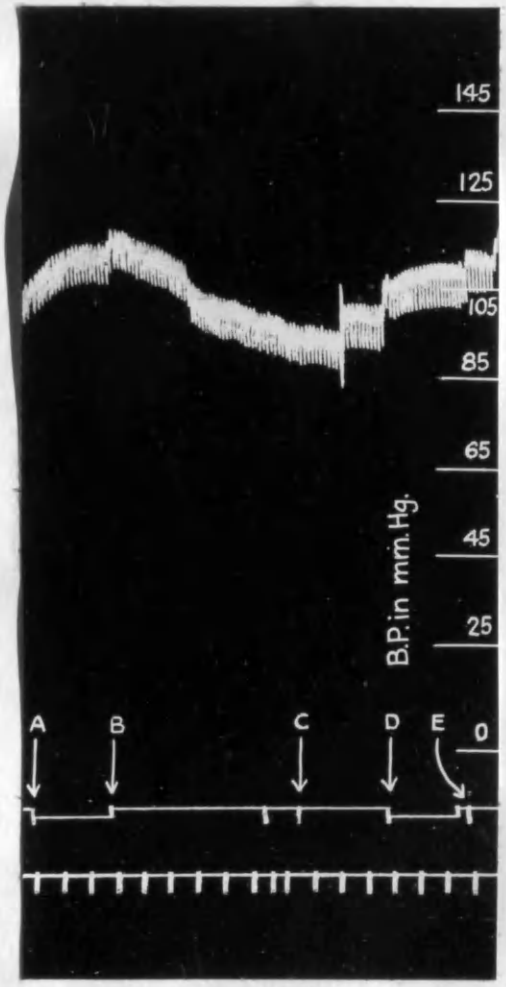
145
125
105
85
65
45
25
0
B.P. in mm. Hg.
A
B
C
D
E

Fig. 38.

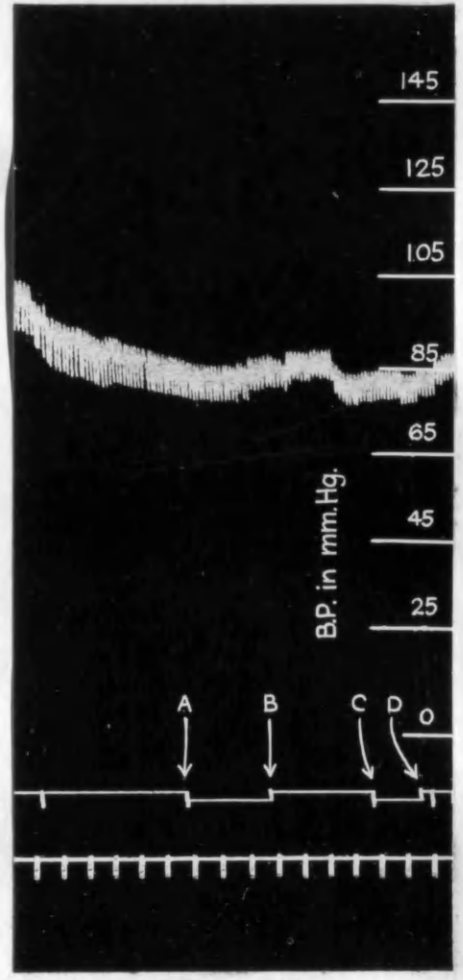
145
125
105
85
65
45
25
0
B.P. in mm. Hg.
A
B
C
D

Fig. 37.

Fig. 39.

Record from a cat weighing 3.5 K.

A. Skull trephined after removal of both stellate ganglia.

Fig. 40.

Record from same cat as Fig. 39, after removal of the stellate ganglia.

A. Slight pressure on brain.

B. Pressure off.

C. Slight pressure on brain.

D. Pressure off.

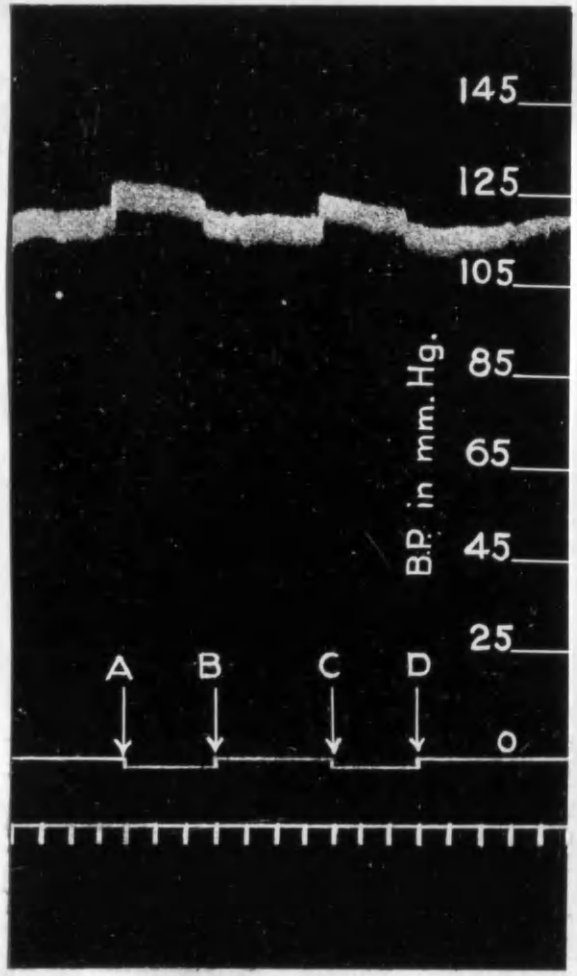
145
125
105
85
65
45
25
0
B.P. in mm. Hg.
A
B
C
D

FIG. 40.

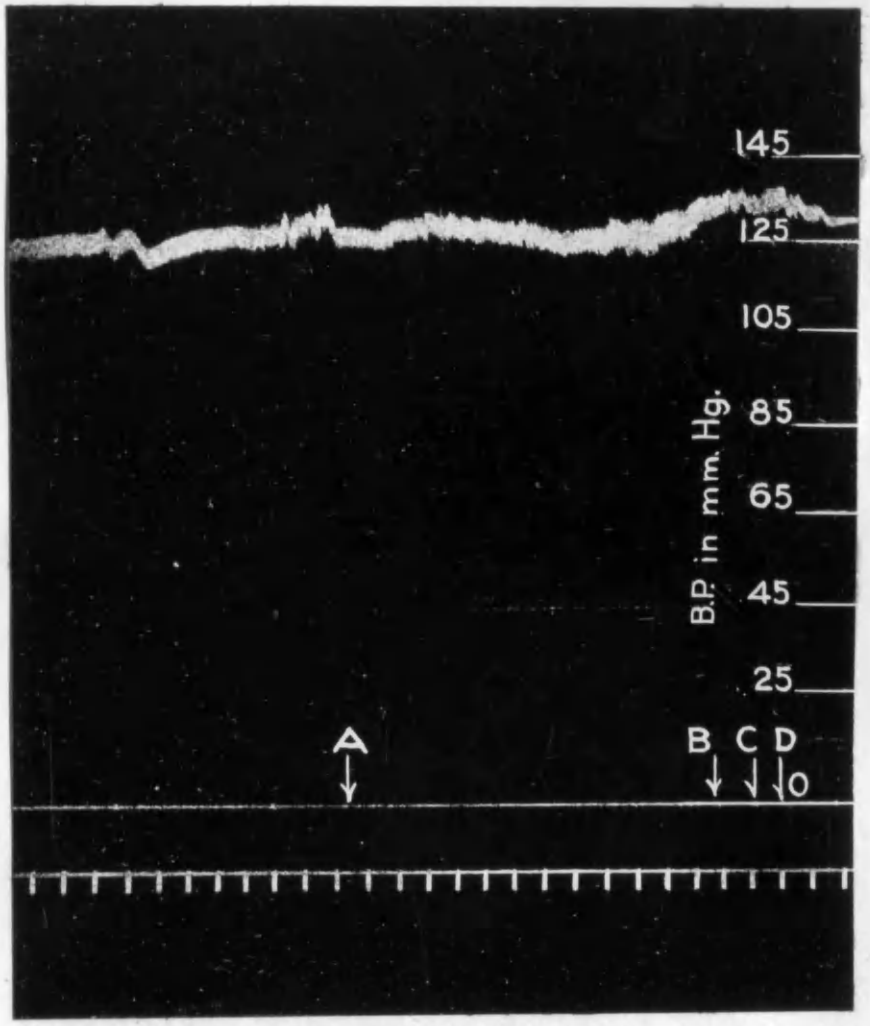
145
125
105
85
65
45
25
0
B.P. in mm. Hg.
A
B
C
D

FIG. 39.

Fig. 41.

Both stellate ganglia removed.

Skull trephined.

Vagi divided.

A. Vagi divided.

B. Pressure on brain.

C. Pressure off.

D. Artificial respiration.

E. Artificial respiration stopped.

Fig. 42.

Shows a repetition of the pro-:cedure in Fig. 41 in the same animal.

A. Pressure on brain.

B. Pressure off.

C. Artificial respiration.

D. Artificial respiration stopped.

E. Pressure on brain.

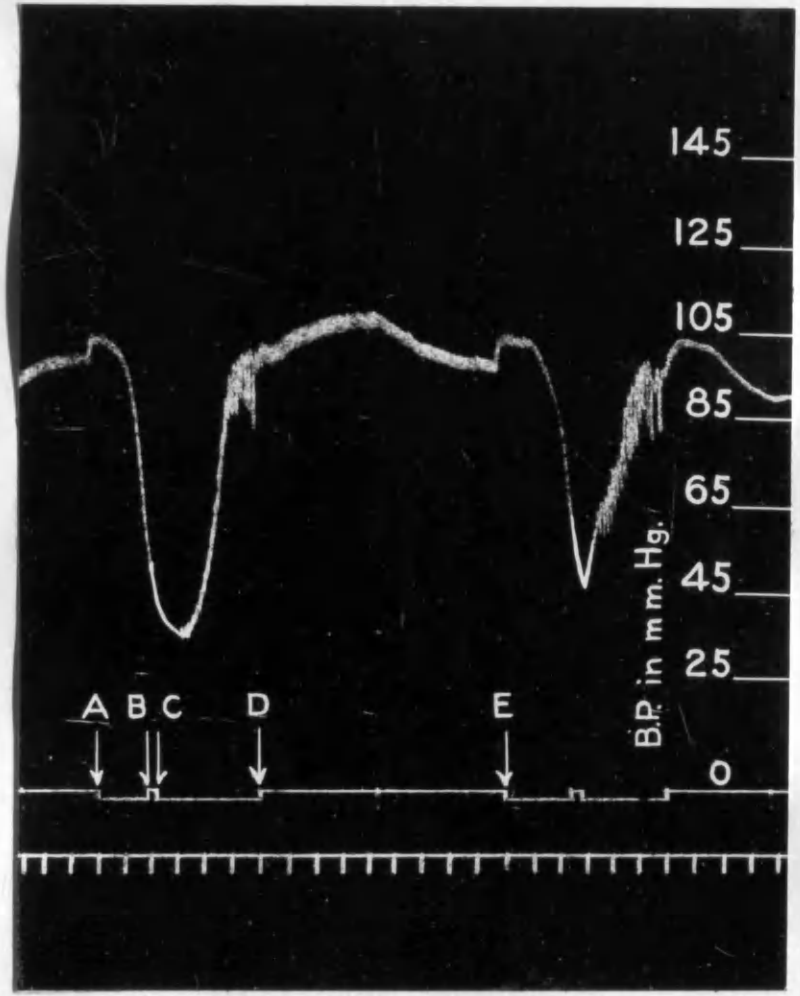
145
125
105
85
65
45
25
0
B.P. in mm. Hg.
A B C D E

Fig. 42.

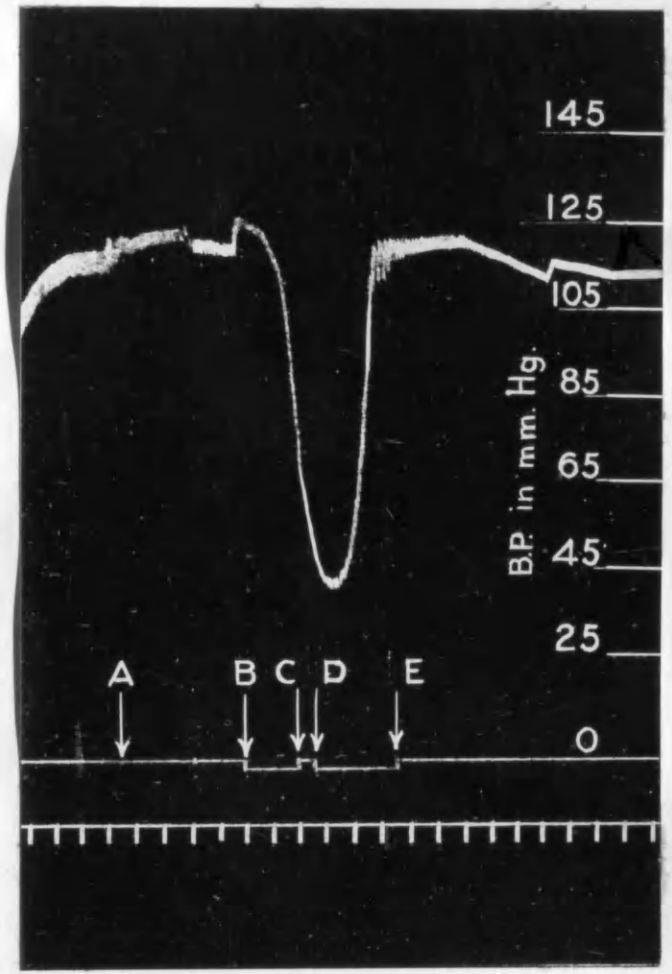
145
125
105
85
65
45
25
0
B.P. in mm. Hg.
A B C D E

Fig. 41.

Fig. 43.

Record from a cat weighing 3 K in which both stellate ganglia were removed, and a record of the intracranial pressure taken shows the effect of suddenly increasing the intracranial pressure and of suddenly lowering it to zero.

Fig. 44.

Record from the same animal as Fig. 43. Shows the effect of gradually raising and gradually lowering the intracranial pressure after removal of the stellate ganglia.

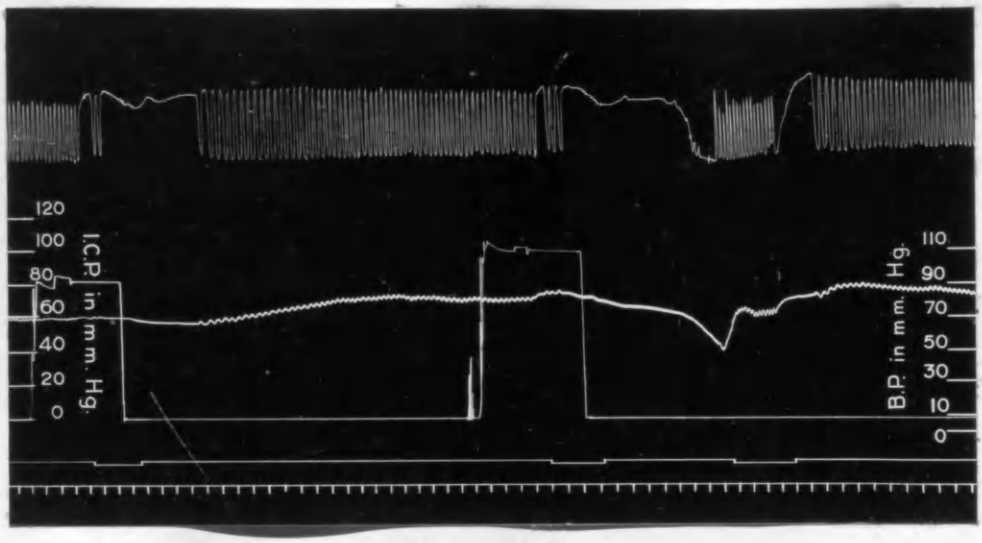
120
100
80
60
40
20
0
I.C.P. in m m. Hg.
110
90
70
50
30
10
0
B.P. in m m. Hg.

Fig. 43.

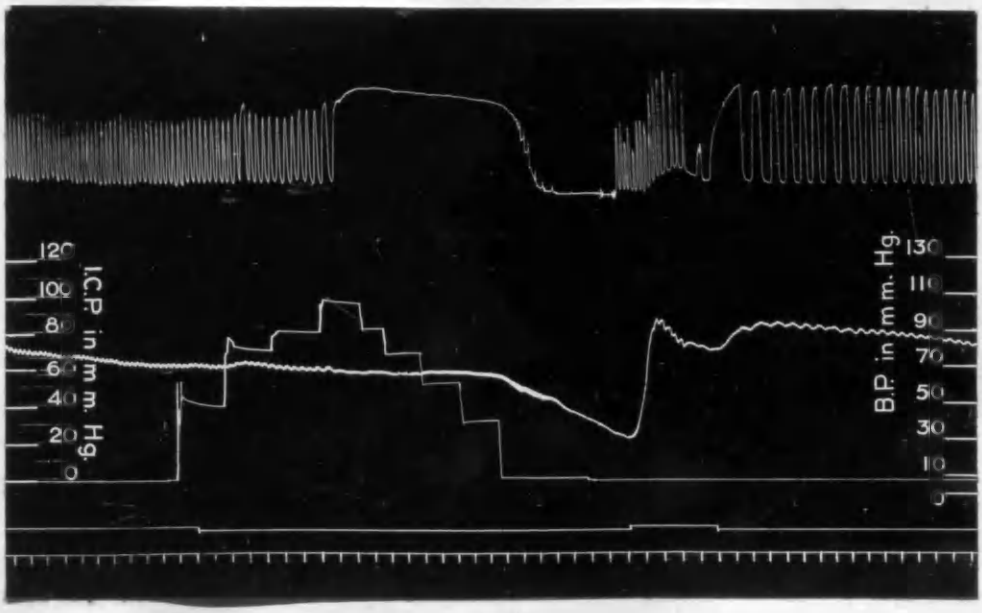
120
100
80
60
40
20
0
I.C.P. in m m. Hg.
130
110
90
70
50
30
10
0
B.P. in m m. Hg.

Fig. 44.

Fig. 45.

Is a record from the same animal. Here the increased intracranial pressure was maintained for some time.

A. Artificial respiration.

B. Artificial respiration stopped.

C. Artificial respiration.

D. Artificial respiration stopped.

Fig. 46.

Is a record from another cat weighing 3 K in which both stellate ganglia were removed. The intracranial pressure was gradually raised and then gradually lowered. Artificial respiration continuous.

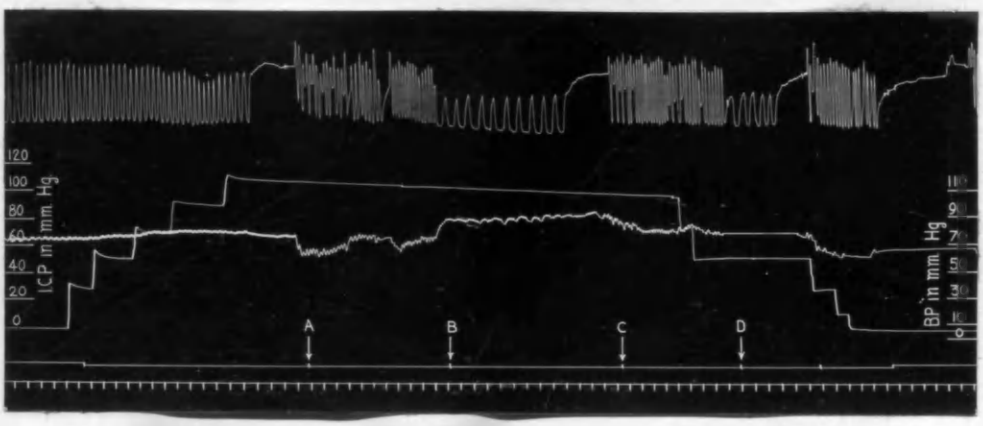
120
100
80
60
40
20
0
ICP in mm Hg
BP in mm Hg
A
B
C
D

FIG. 45.

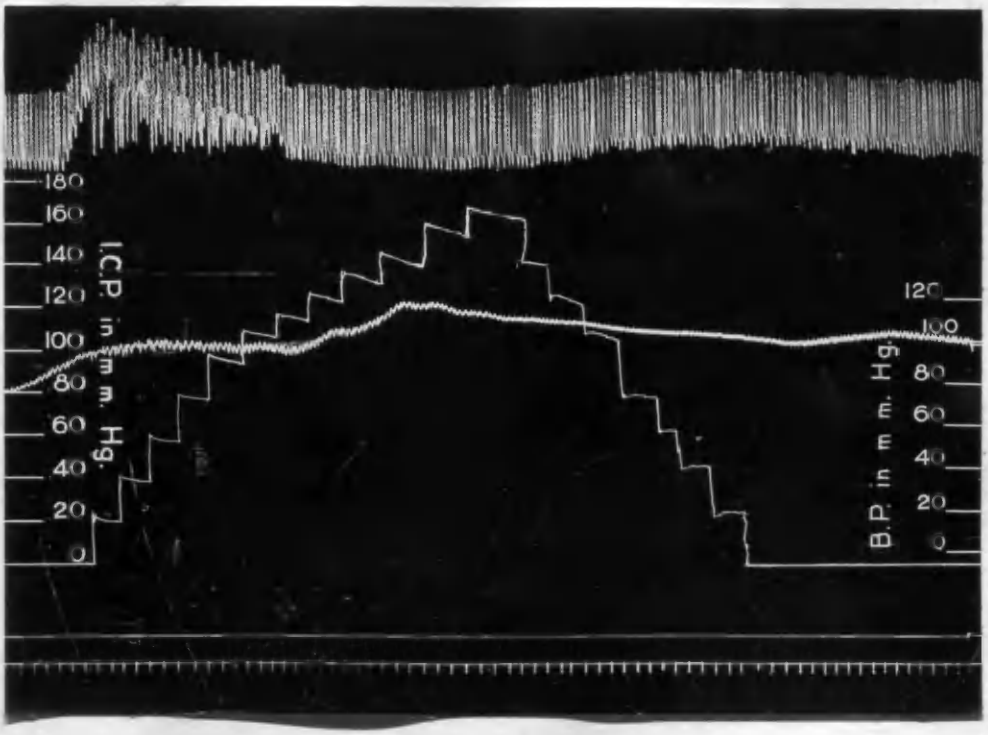
180
160
140
120
100
80
60
40
20
0
I.C.P. in m m. Hg.
120
100
80
60
40
20
0
B.P. in m m. Hg.

FIG. 46.

Fig. 47.

Record from another cat in which both stellate ganglia were removed, and the intracranial pressure grad-:ually raised and then gradually lowered.

Fig. 48.

Shows the same procedure as in Fig. 47. Here again both stellate ganglia had been pre-:viously removed.

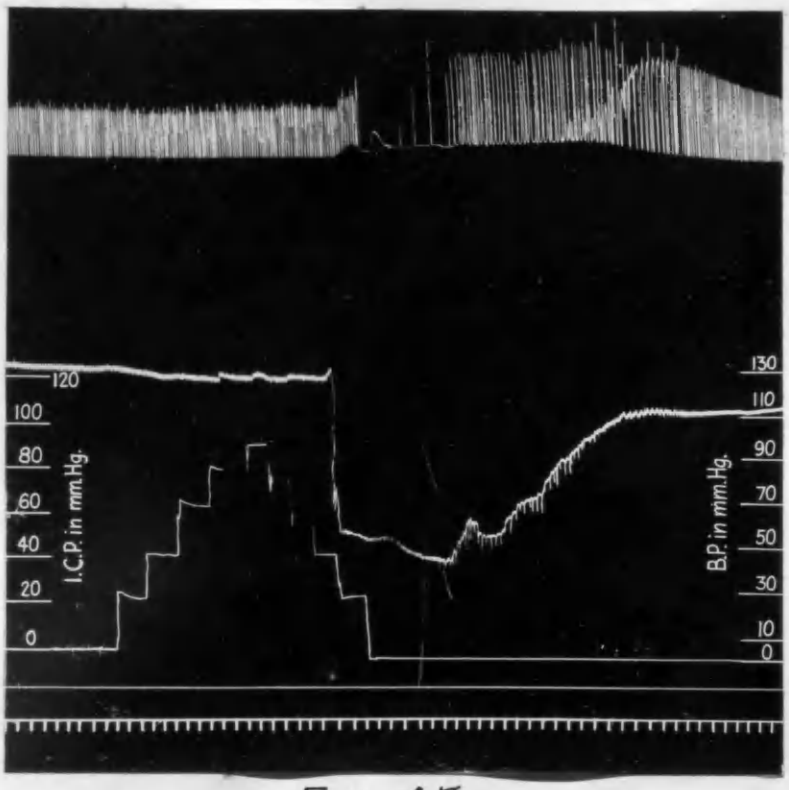
120
100
80
60
40
20
0
I.C.P. in mm.Hg.
130
110
90
70
50
30
10
0
B.P. in mm.Hg.

FIG. 47.

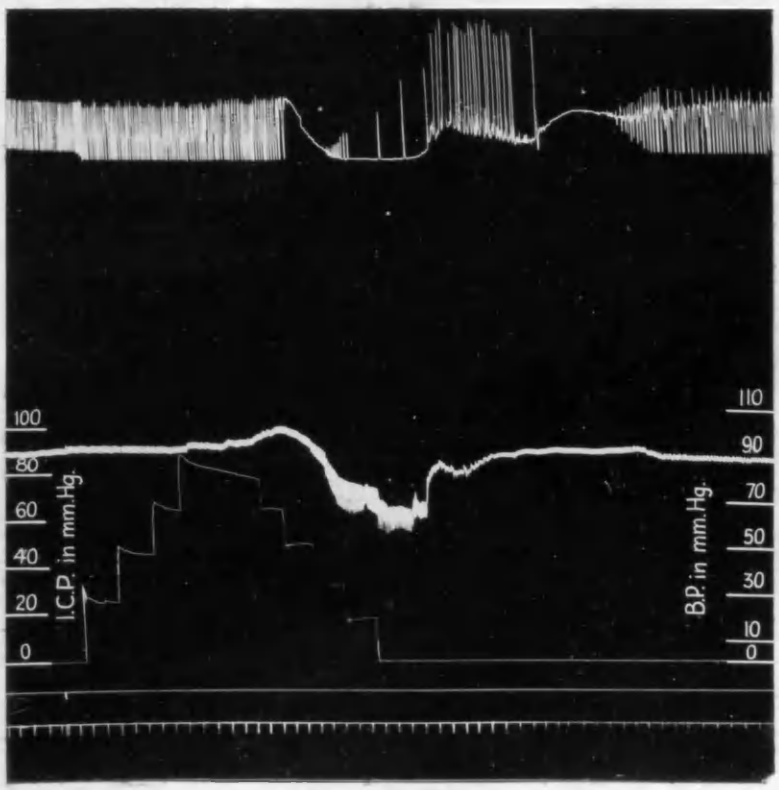
100
80
60
40
20
0
I.C.P. in mm.Hg.
110
90
70
50
30
10
0
B.P. in mm.Hg.

FIG. 48.

Fig. 49.

In addition to the removal of both stellate ganglia, the vagi were divided.

Fig. 50.

Record from a cat weighing 2.9 K. In this animal the stellate ganglia were removed and the vagi divided before the intracranial pressure was raised.

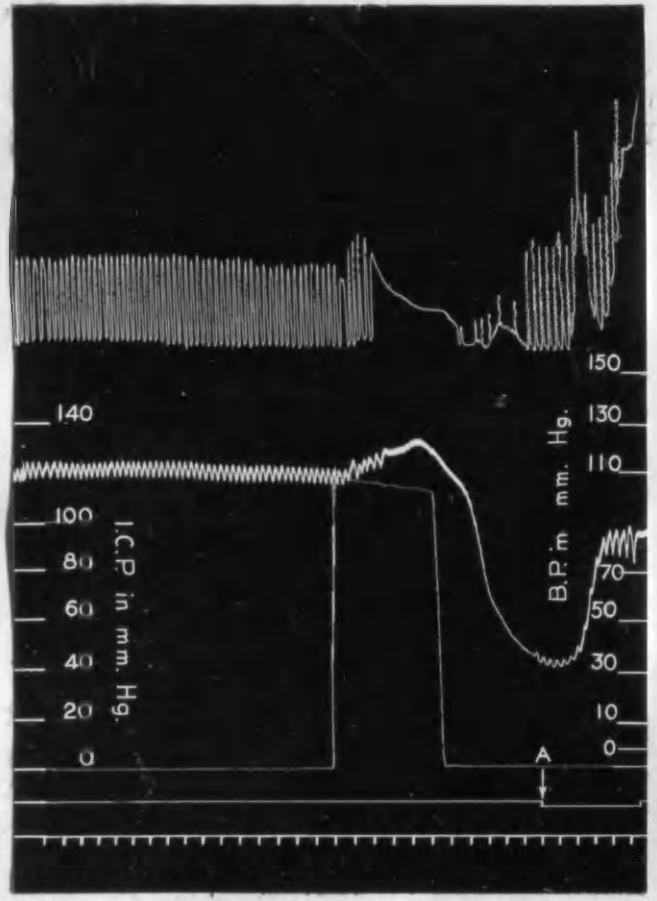
150
140
130
110
100
80
60
40
20
0
I.C.P. in mm. Hg.
B.P. in mm. Hg.
70
50
30
10
0
A

Fig. 50.

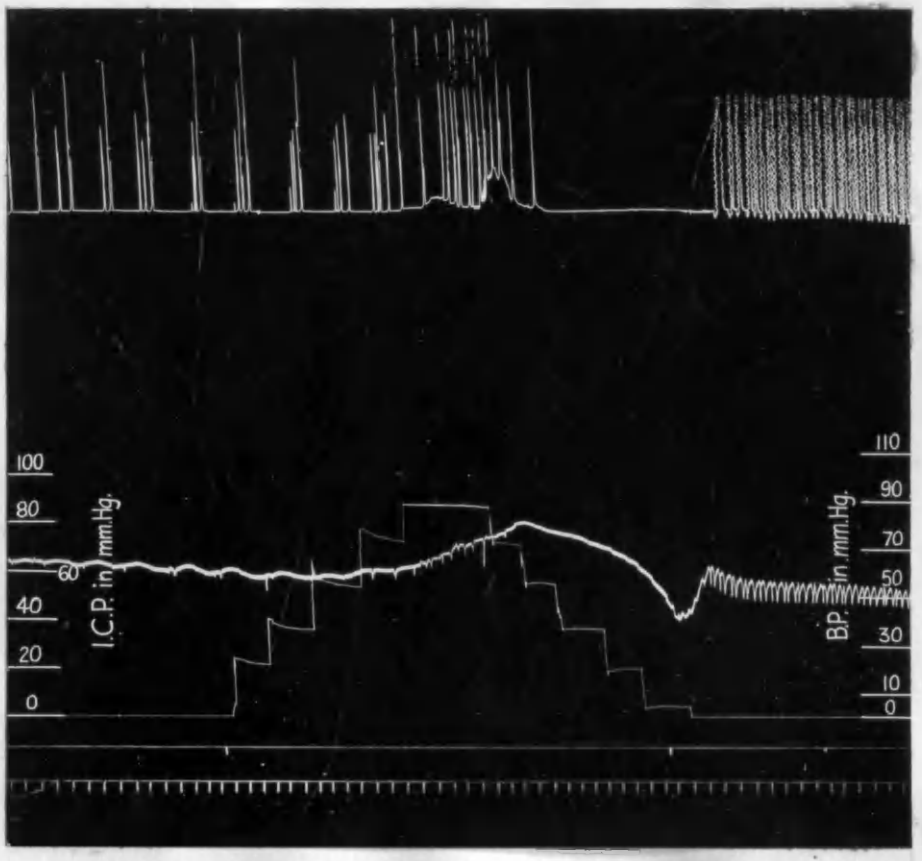
110
100
90
80
70
60
50
40
30
20
10
0
I.C.P. in mm.Hg.
B.P. in mm.Hg.

Fig. 49.

Fig. 51.

Record from a cat weighing 2.1 K. In this animal the stellate ganglia were removed and vagi were divided before the intracranial pressure was raised.

Fig. 52.

Is from the same animal as Fig. 51., at a later stage in the experiment, but here the intracranial pressure was suddenly lowered to zero.

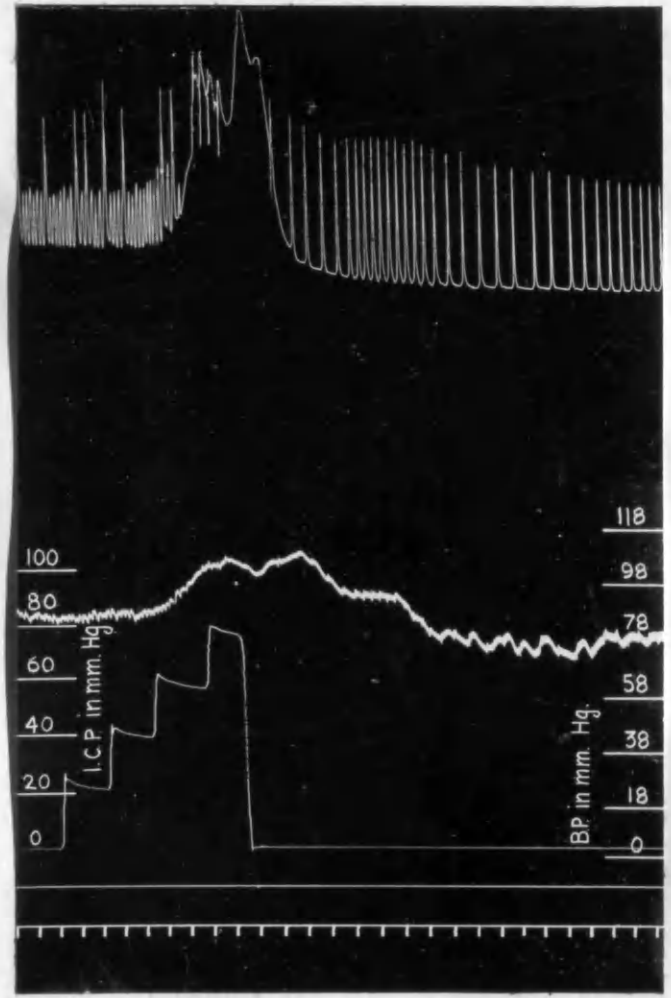
100
80
60
40
20
0
I.C.P. in mm. Hg.
118
98
78
58
38
18
0
B.P. in mm. Hg.

Fig. 52.

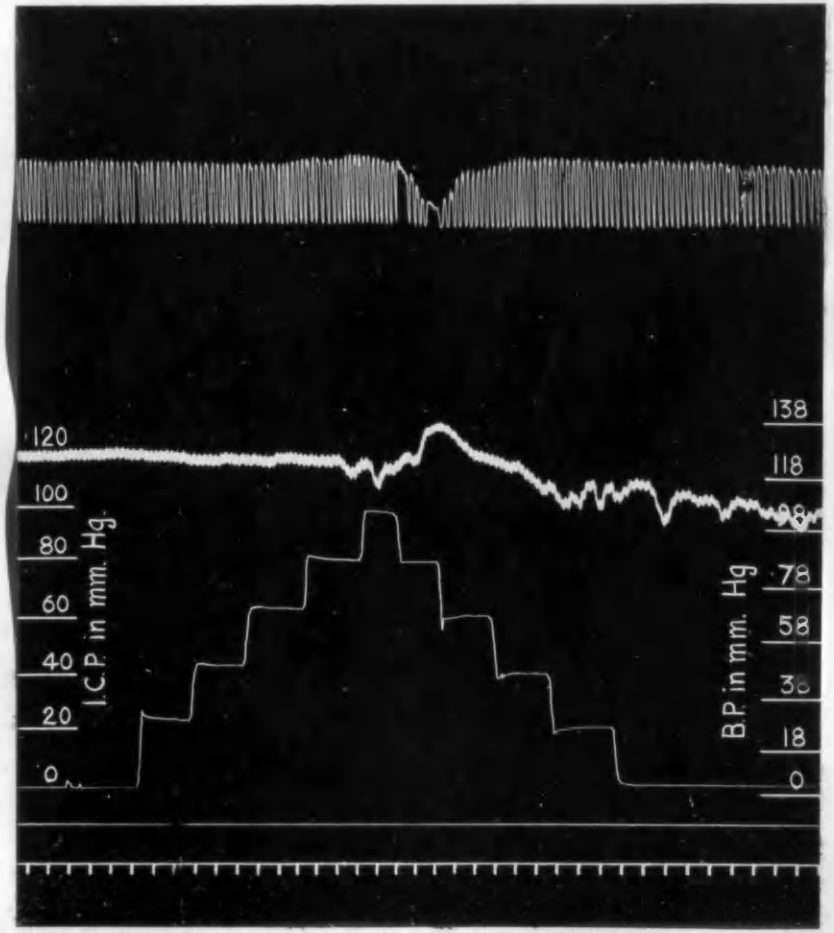
120
100
80
60
40
20
0
I.C.P. in mm. Hg.
138
118
98
78
58
38
18
0
B.P. in mm. Hg

Fig. 51.

Fig. 53.

Is from the same animal as Fig. 51, but here artificial respiration was continuous.

Fig. 54.

Record from a decerebrate cat, weighing 4.4 K.

In A, the first arrow indicates the intravenous injection of 0.5 cc. of extract of the cat's own brain.

In B, the first arrow indicates the injection of the same dose as in A.

In C, the first arrow indicates the injection of 0.5 cc. extract of the brains of other 2 cats.

In this case the dried extract had been prepared 5 days previously.

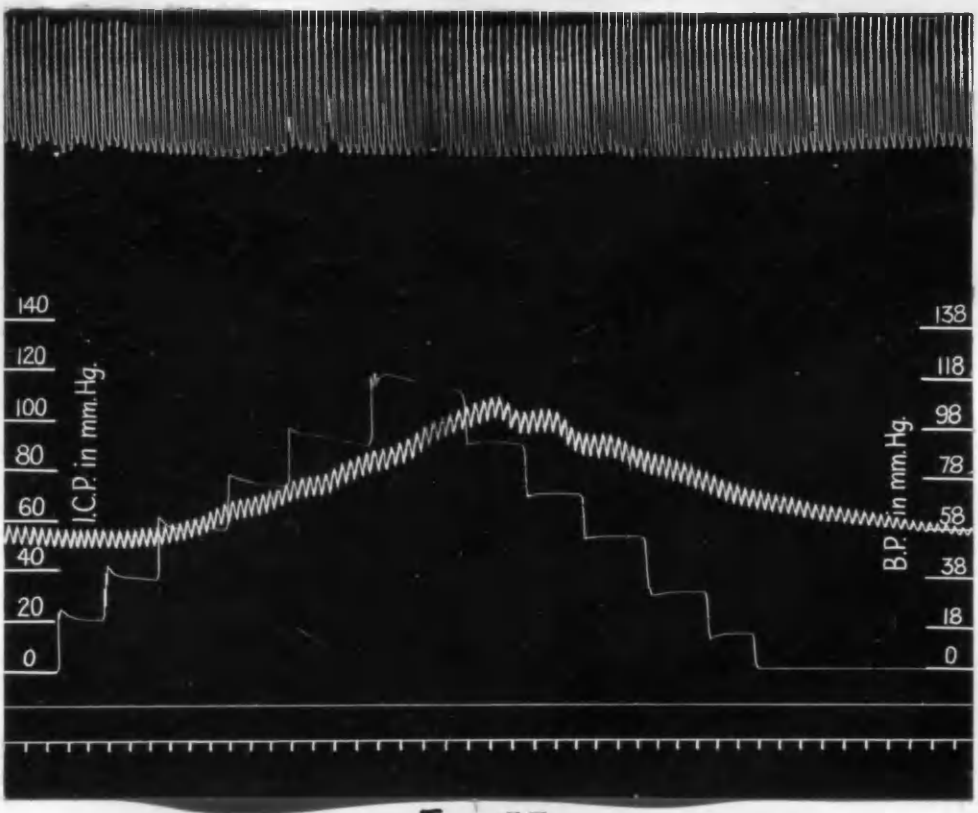
140
120
100
80
60
40
20
0
I.C.P. in mm.Hg.
138
118
98
78
58
38
18
0
B.P. in mm.Hg.

FIG. 53

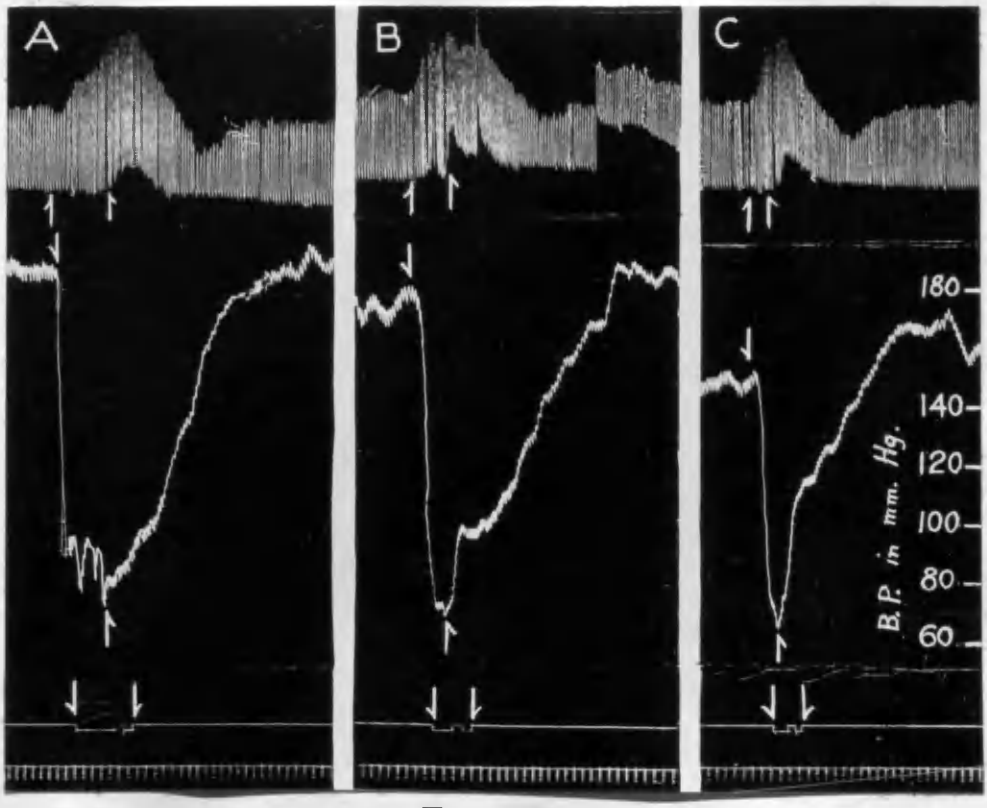
A
B
C
180
140
120
100
80
60
B.P. in mm. Hg.

FIG. 54.

Fig. 55.

Record from a decerebrated cat weighing 3.6 K.

A. Intravenous injection of 0.5 cc. of brain extract.

B. Intravenous injection of 1 cc. of saline.

Fig. 56.

Record from the same animal

A. Intravenous injection of 1 cc. of brain extract.

B. Intravenous injection of 1 cc. of saline.

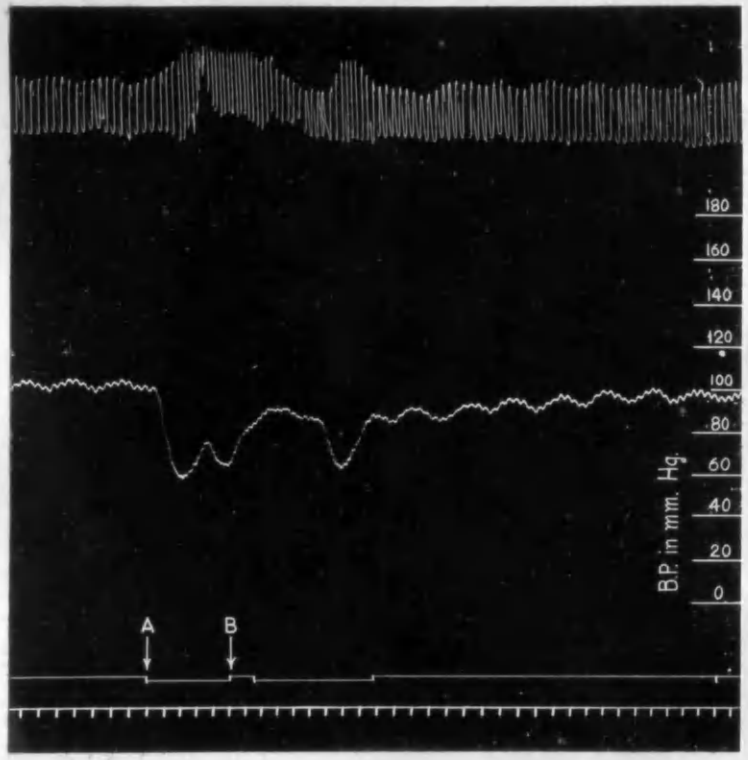
180
160
140
120
100
80
60
40
20
0
B.P. in mm. Hg.
A
B

FIG. 56.

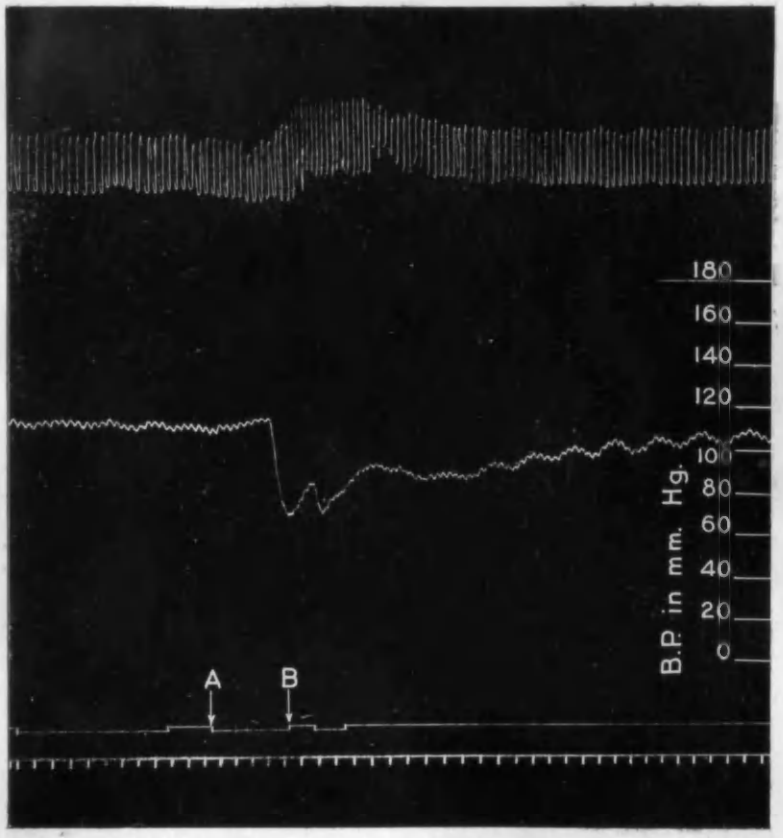
180
160
140
120
100
80
60
40
20
0
B.P. in mm. Hg.
A
B

FIG. 55.

Fig. 57.

Record from the same animal. The animal being decerebrate was get-: ting no anaesthetic, but at this stage it was given intratracheal ether for some time, and the ether was then blown off.

A. Intravenous injection of 0.5 cc. of brain extract.

B. Intravenous injection of 1 cc. of saline.

Fig. 58.

Record from a cat weighing 3.4 K. This animal was not decerebrated.

A. Intravenous injection of 0.25 cc. of brain extract.

B. Drum stopped.

C. Intravenous injection of 0.25 cc. of brain extract, after treatment with Norit.

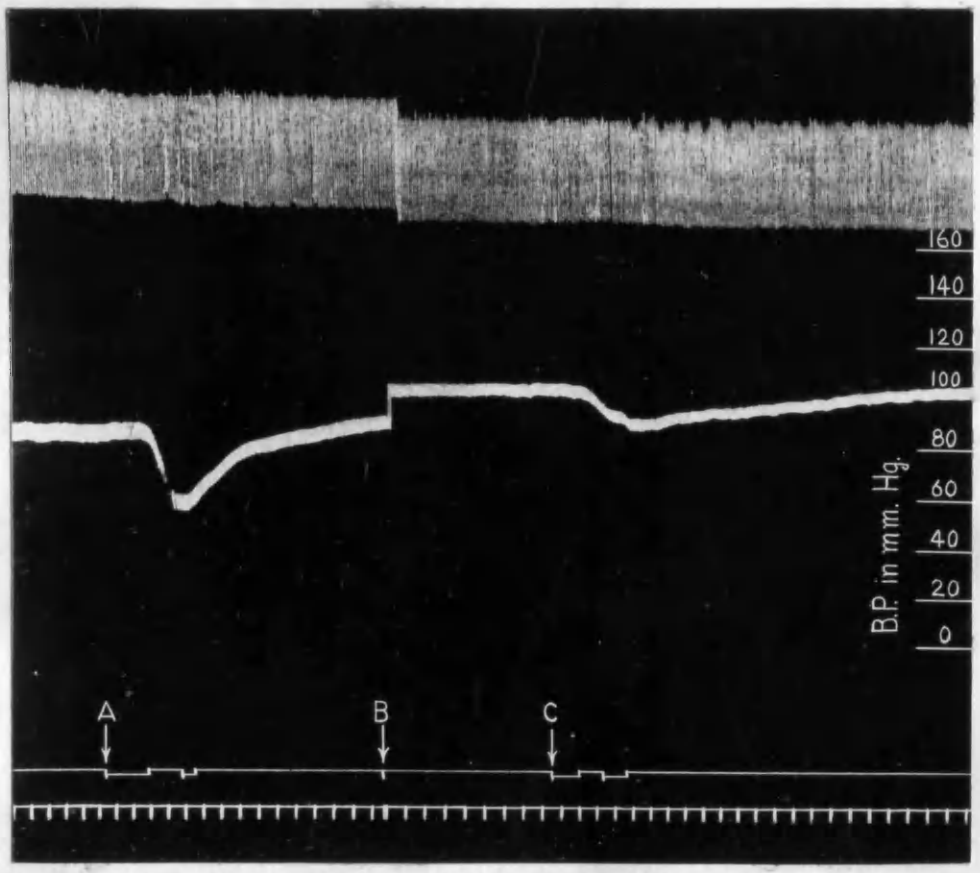
160
140
120
100
80
60
40
20
0
B.P. in mm. Hg.
A
B
C

FIG. 58.

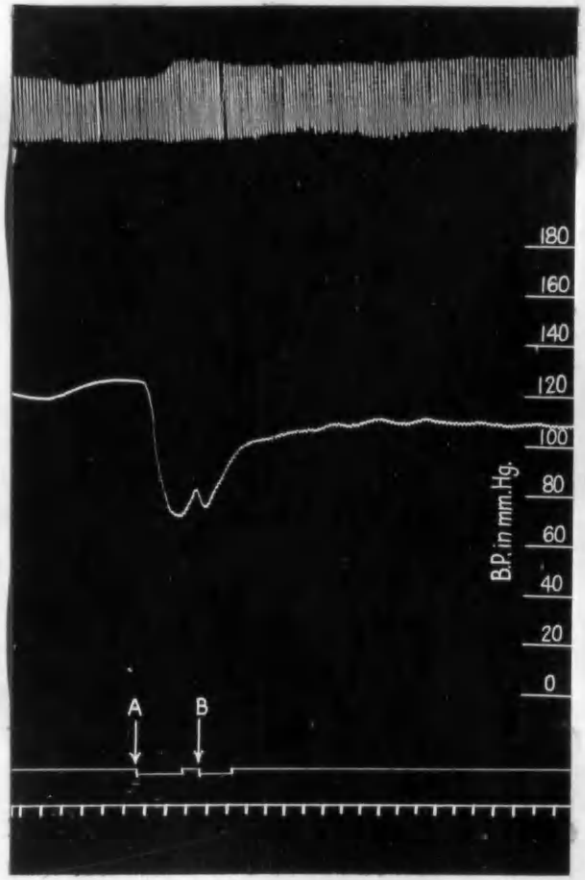
180
160
140
120
100
80
60
40
20
0
B.P. in mm. Hg.
A
B

FIG. 57.

Fig. 59.

Is a record from the same cat.

A. Intravenous injection of 0.5 cc. of brain extract.

B. Intravenous injection of 0.5 cc. saline.

C. Intravenous injection of 1 cc. of brain extract.

D. Intravenous injection of 0.5 cc. saline.

Fig. 60.

Both vagi were divided some time previously.

A. Intravenous injection of 1 cc. of brain extract.

B. Intravenous injection of 0.5 cc. saline.

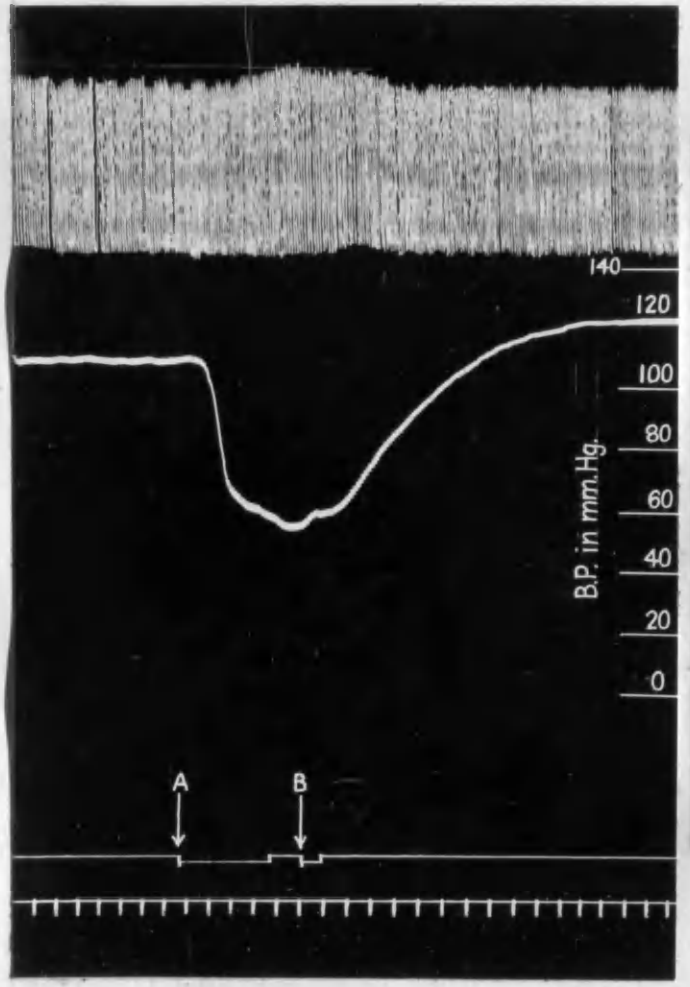
140
120
100
80
60
40
20
0
B.P. in mm.Hg.
A
B

Fig. 60.

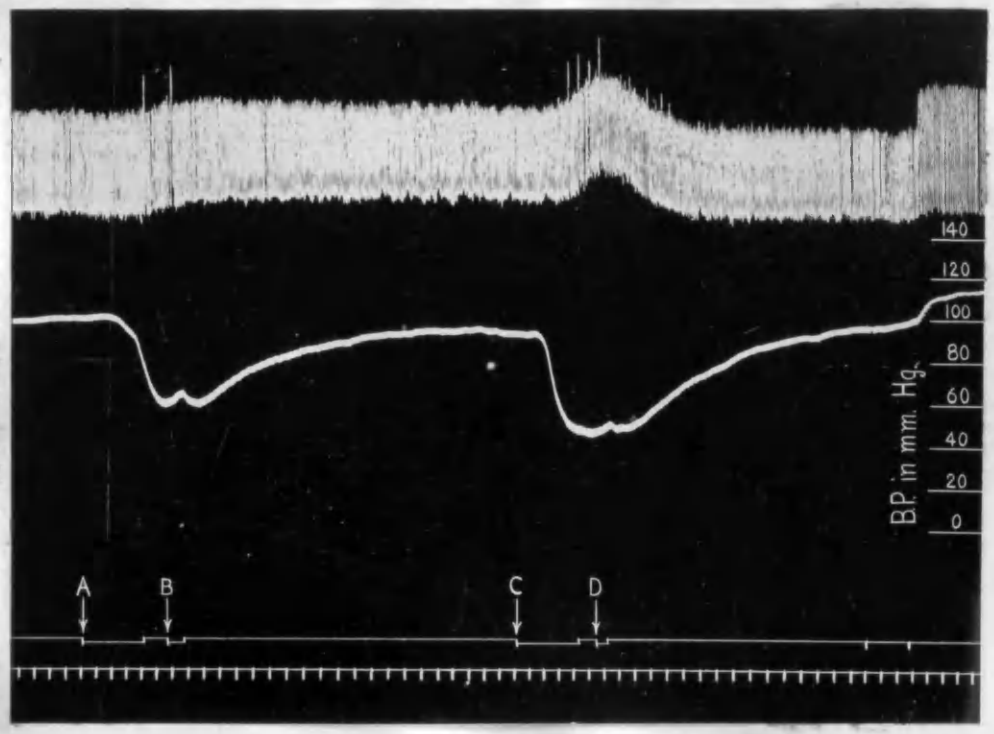
140
120
100
80
60
40
20
0
B.P. in mm. Hg.
A
B
C
D

Fig. 59.

Fig. 61.

Record from a cat weighing 2.4 K.

A. Intravenous injection of a very small dose of an extract prepared from a crushed limb.

B. Intravenous injection of a larger dose of the same extract.

C. Intravenous injection of 0.00002 mg.of histamine.

D. Repetition of C.

Fig.62.

Record from a cat, weighing 3.6 K.

A. Intravenous injection of 0.3 cc. of a 1 in 100,000 solution of histamine.

B. Drum stopped.

C. Intravenous injection of 0.3 cc. of a 1 in 100,000 solution of histamine after treatment with Norit.

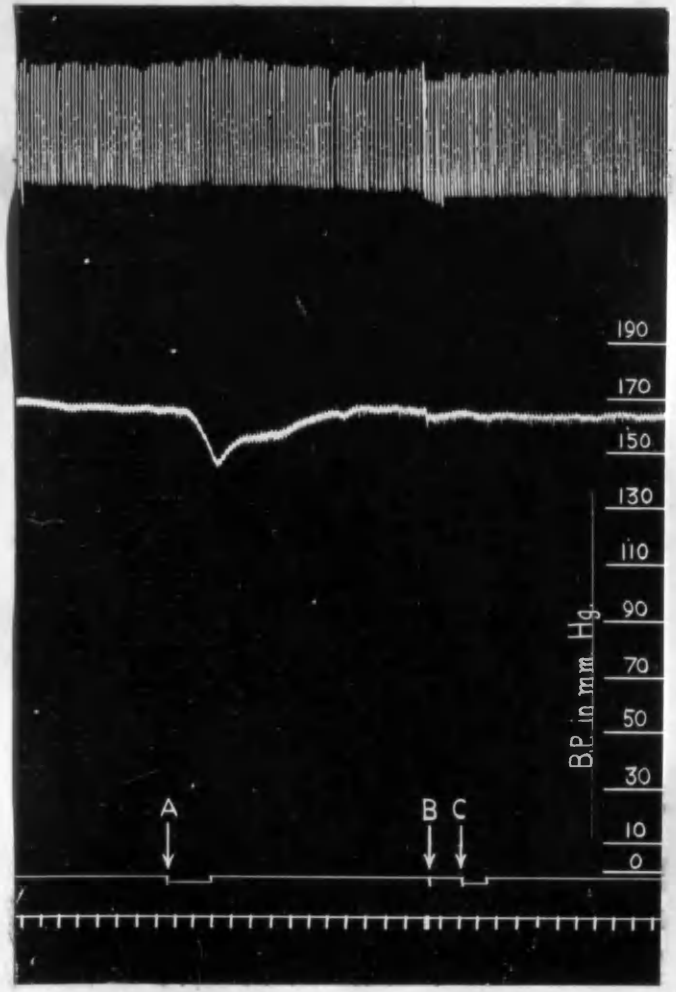
190
170
150
130
110
90
70
50
30
10
0
B.P. in mm. Hg.
A
B C

Fig. 62.

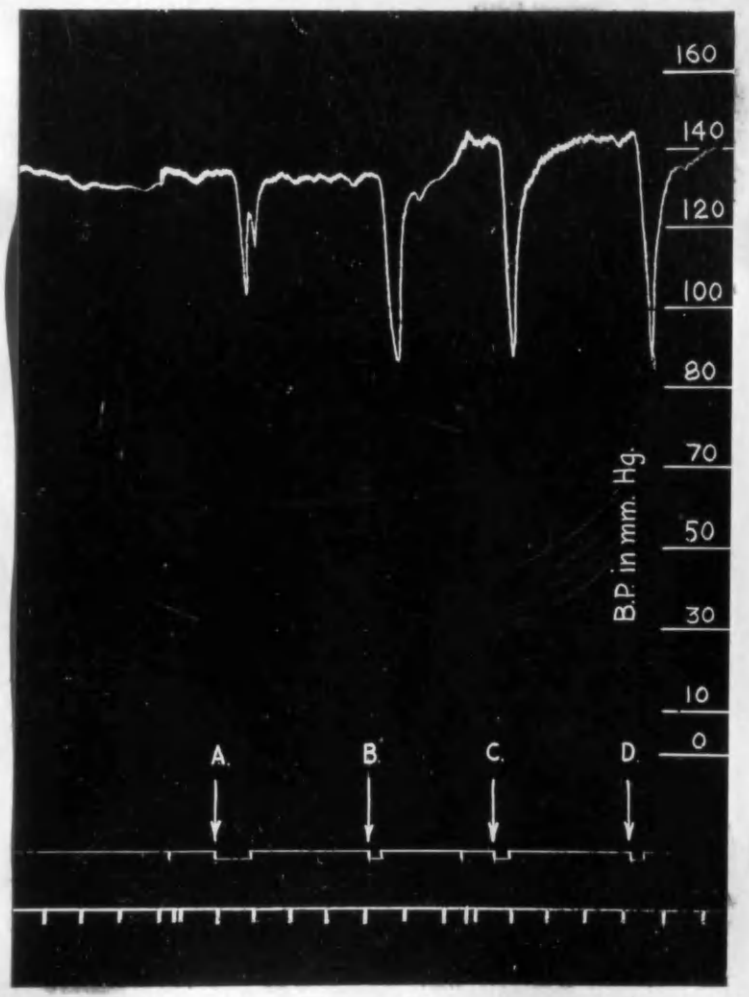
160
140
120
100
80
70
50
30
10
0
B.P. in mm. Hg.
A.
B.
C.
D.

Fig. 61.

Fig. 63.

Record from a cat weighing 3.4 K.

A. Intravenous injection of 0.25 cc. of brain extract.

B. Injection of same dose of brain extract after treatment with Norit.

Fig. 64.

Record from a cat weighing 3 K.

A. Intravenous injection of 0.5 cc. of brain extract.

B. Intravenous injection of 1 cc. of saline.

C. Intravenous injection of 0.5 cc. of brain extract, after treatment with Norit.

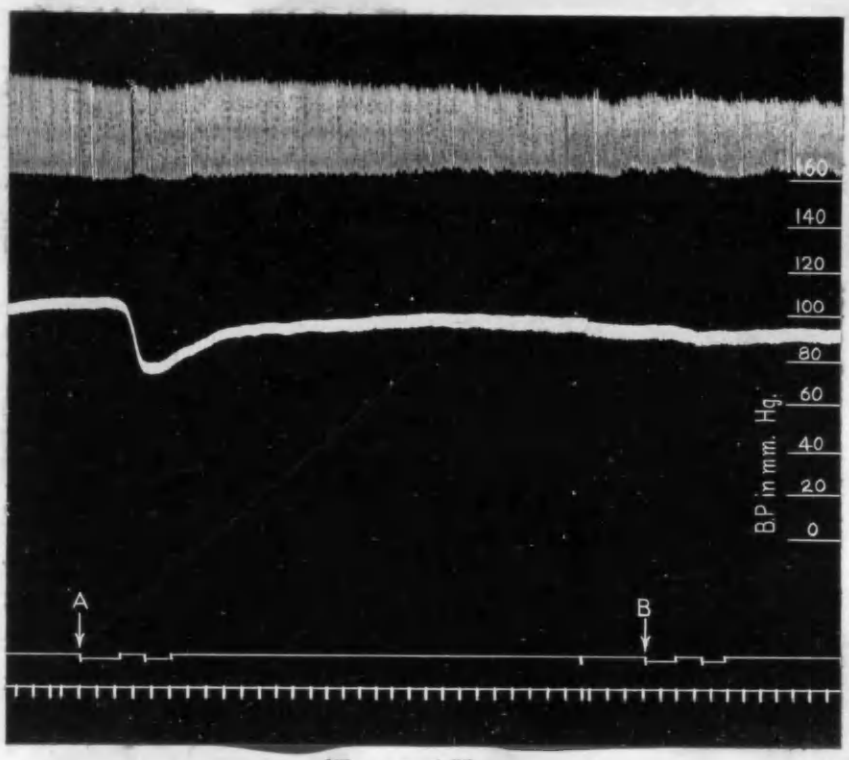
160
140
120
100
80
60
40
20
0
B.P in mm. Hg.
A
B

Fig. 63.

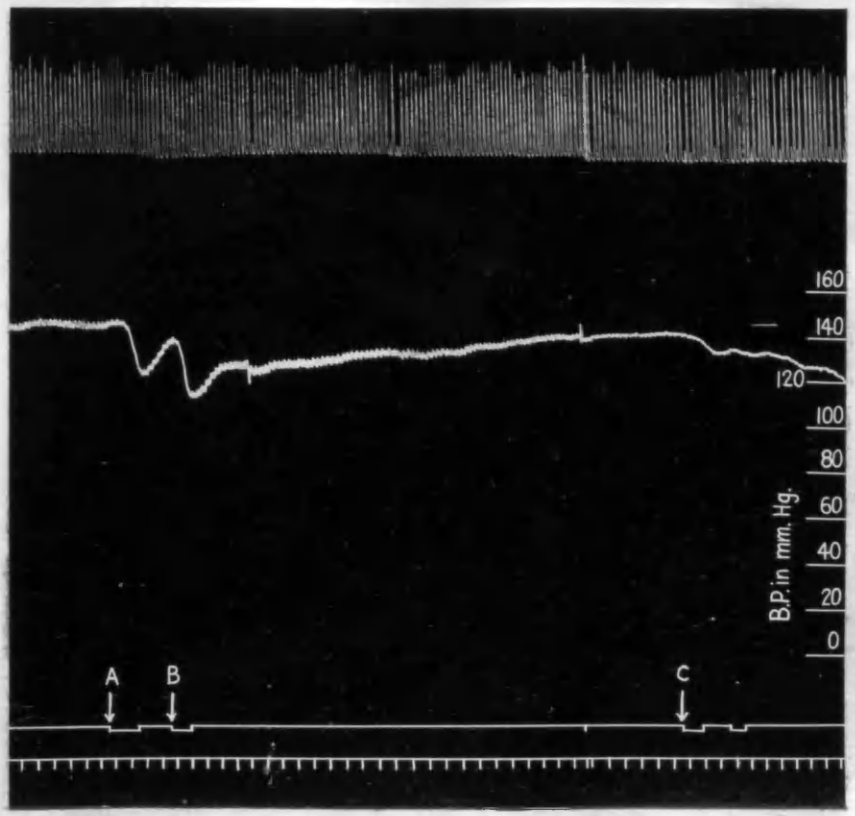
160
140
120
100
80
60
40
20
0
B.P. in mm. Hg.
A
B
C

Fig. 64.

Fig. 65.

Record from a cat weighing 3.2 K.

A. Intravenous injection of 0.5 cc. of brain extract.

B. Intravenous injection of the same dose, after treat-: ment with Norit.

Fig. 66.

Record from the same cat as Fig.65.

A. Intravenous injection of 1 cc. of brain extract.

B. Intravenous injection of the same dose, after treat-: ment with Norit.

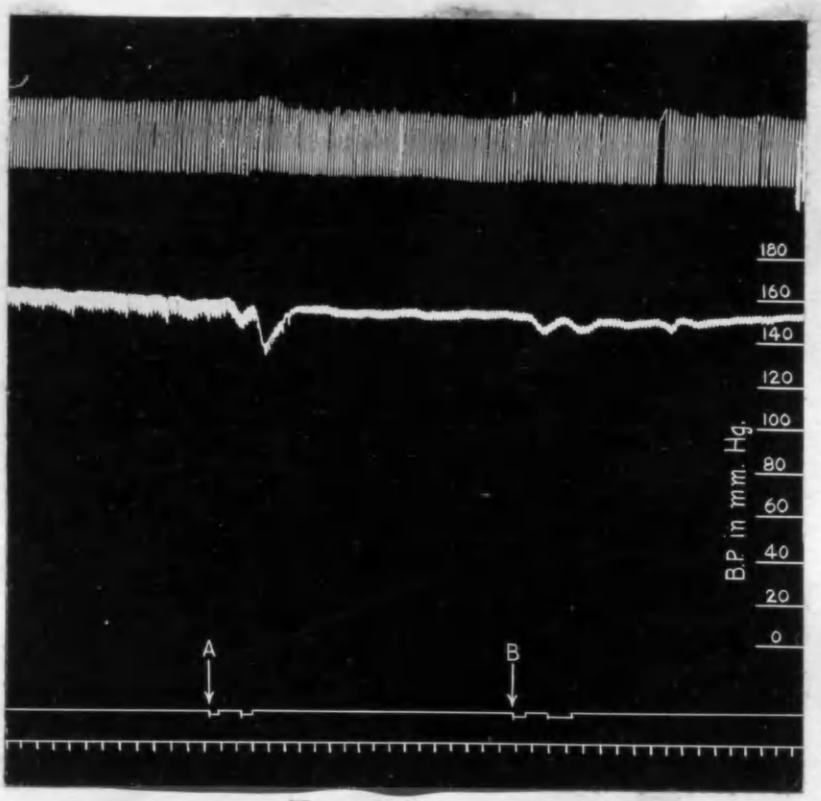
180
160
140
120
100
80
60
40
20
0
B.P. in mm. Hg.
A
B

FIG. 65.

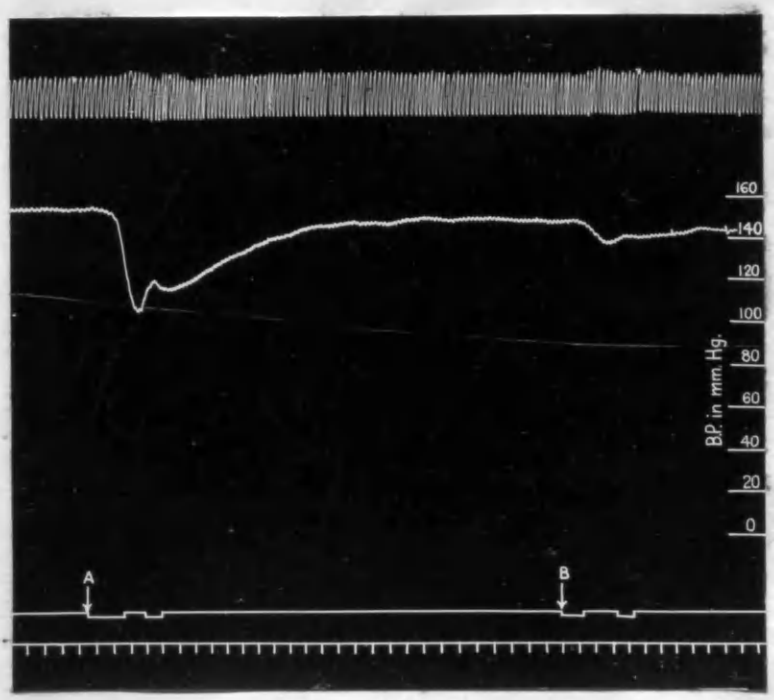
160
140
120
100
80
60
40
20
0
B.P. in mm. Hg.
A
B

FIG. 66.

Fig. 67.

Shows at A, the intravenous injection of 0.5 cc. of brain extract, after treatment with Norit.

Fig. 68.

Record from a cat weighing 2.3 K.

A. Intravenous injection of 0.3 cc. of brain extract.

B. Intravenous injection of same dose, after treat-
: ment with Norit.

C. Shows the effect of stimu-
: lating the vagus with the coil at 8.5 cm.

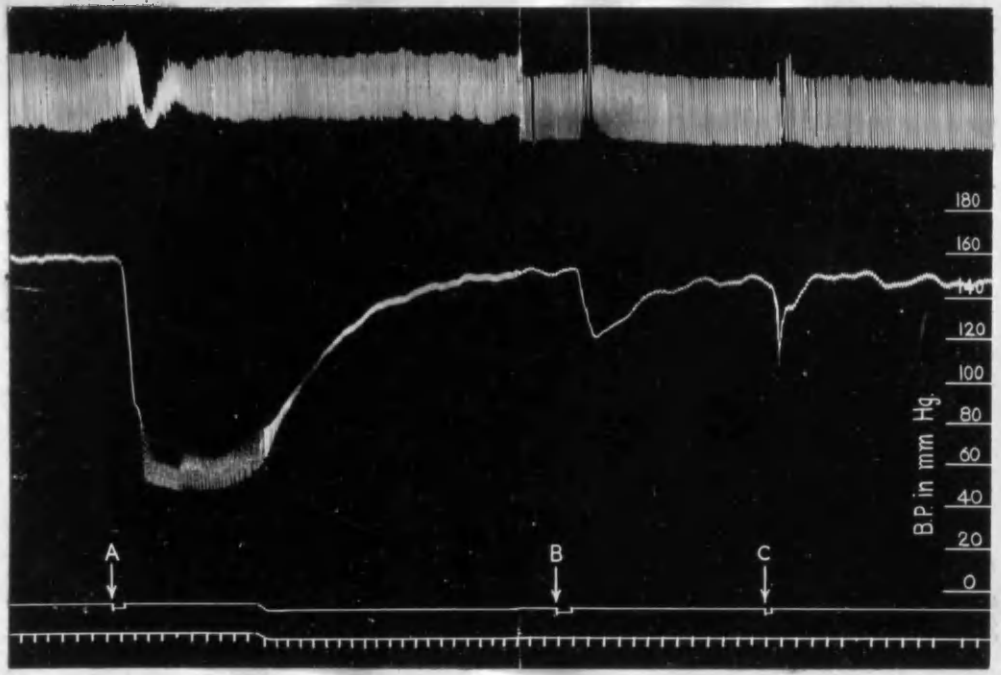
180
160
140
120
100
80
60
40
20
0
B.P. in mm Hg.
A
B
C

FIG. 68.


180
160
140
120
100
80
60
40
20
0
B.P. in mm.Hg.
A

FIG. 67.

Fig. 69.

Trendelenburg apparatus.

(1) Inner vessel with nutrient fluid and tissue.
(2) Outer reservoir with hot water.
(3) Outlet from inner vessel.
(4) Aerater with curved end to fasten tissue.
(5) Capillary tubing as valve from pressure bottle.
(6) (6a) Screw clamps.
(7) Pressure bottle with mixture of CO_2 and O_2.
(8) Lamp house to keep constant temperature.
(9) Carbon filament lamp.
(10) Vessel used for fluid.
(11) Frontal writing lever.
(12) Hedgehog quill point.
(13) Thermometer.

A. Plan of lever arrangement to show method used to get maximum range without fouling. Lever mounted on separate stand for easier adjustment.

Fig. 70.

Cornu of the uterus of a virgin guinea pig in the bath.

A. The addition to the bath of a 1 in 1,800,000 solution of histamine.

B. The addition to the bath of 0.5 cc. of brain extract.

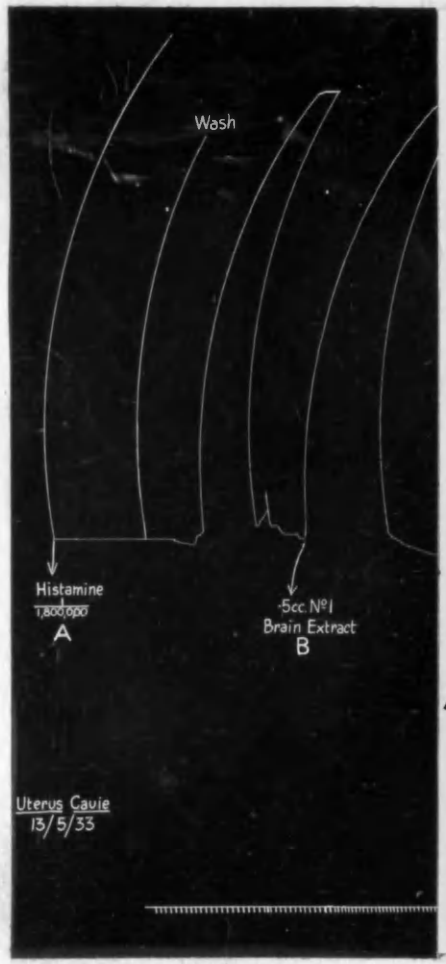
Wash
Histamine
1/1,800,000
A
·5cc. N°1
Brain Extract
B
Uterus Cavie
13/5/33

Fig. 70.

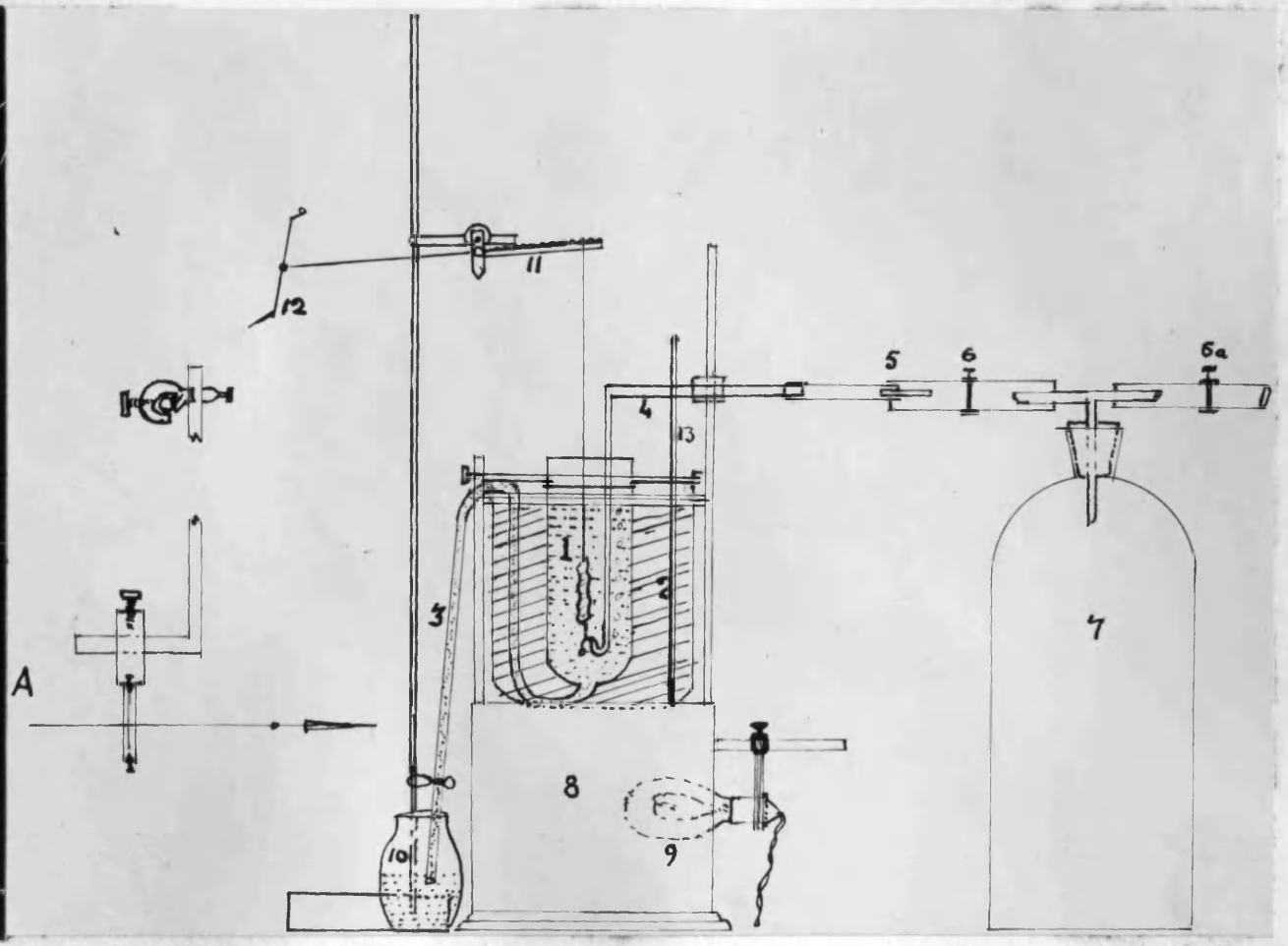
A
1
2
3
4
5
6
6a
7
8
9
10
11
12
13

Fig. 69.

Fig. 71.

Cornu of the uterus of a virgin guinea pig in the bath.

(1) The addition to the bath of a 1 in 10,000,000 solution of histamine.

(2) Bath washed out.

(3) Addition of 1 cc. of brain extract.

(4) Bath washed out.

(5) Addition of 1 cc. of brain extract.

(6) Bath washed out.

Fig. 72.

Cornu of the uterus of a virgin guinea pig in the bath.

(1) A 1 in 10,000,000 solution of histamine added to the bath.

(2) Bath washed out.

(3) 1 cc. of No. 1 brain extract added to the bath.

(4) Bath washed out.

(5) 1 cc. of No. 2 brain extract added to the bath.

(6) Bath washed out.

(7) 1 cc. of No. 1 brain extract, after treatment with Norit, added to the bath.

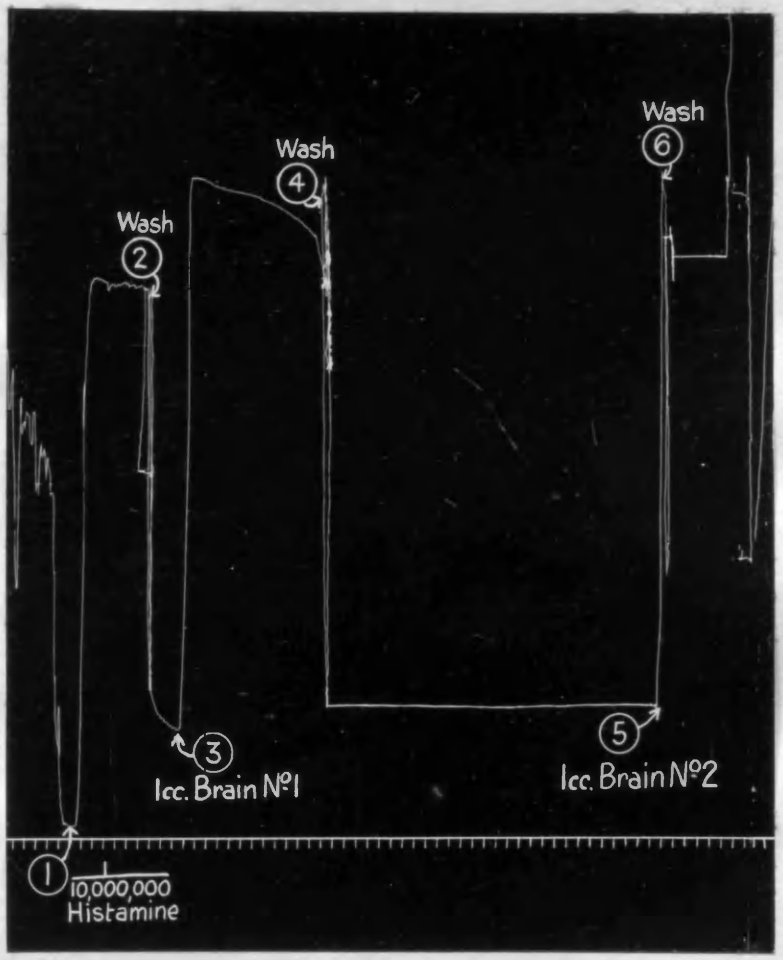
Wash
6
Wash
4
Wash
2
3
Icc. Brain Nº1
5
Icc. Brain Nº2
1
10,000,000
Histamine

Fig. 71.

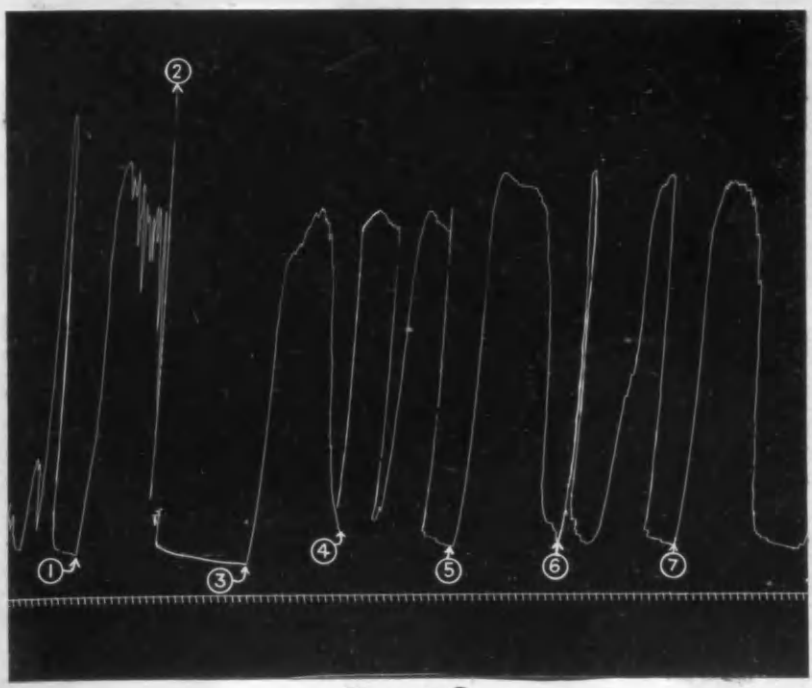
2
1
3
4
5
6
7

Fig. 72.

Fig. 73.

Cornu of the uterus of a virgin guinea pig in the bath.

(1) 0.5 cc. of a 1 in 10,000,000 solution of histamine added to the bath.
(2) Bath washed out.
(3) 0.25 cc. of brain extract added.
(4) Bath washed out.
(5) 0.25 cc. of brain extract, after treatment with Norit, added.
(6) 1 cc. of a 1 in 100,000 solution of atropine added.
(7) Bath washed out.
(8) 0.008 gm. acetyl choline added.
(9) 3 cc. of a 1 in 100,000 solution of atropine added.

Fig. 74.

Cornu of the uterus of a virgin guinea pig in the bath.

(1) 0.25 cc. of a 1 in 1,000,000 solution of histamine added.
(2) Bath washed out.
(3) 0.25 cc. of brain extract added.
(4) Bath washed out.
(5) 0.25 cc. of brain extract, after treatment with Norit, added.
(6) Bath washed out.
(7) 0.25 cc. of a 1 in 1,000 solution of atropine sulphate added.
(8) 0.25 cc. of brain extract, after treatment with Norit, added.
(9) Bath washed out.
(10) 0.000156 gm. acetyl choline added.
(11) Bath washed out.
(12) 0.000156 gm. acetyl choline, after treatment with Norit, added.
(13) Bath washed out.
(14) Repetition of (12).
(15) Bath washed out.
(16) 0.000156 gm. acetyl choline added.
(17) Bath washed out.
(18) 0.25 cc. of a 1 in 1,000 solution of atropine sulphate added.
(19) 0.000156 gm. acetyl choline added.
(19a) Bath washed out.
(20) 0.000156 gm. acetyl choline, after treatment with Norit, added.
(21) Bath washed out.

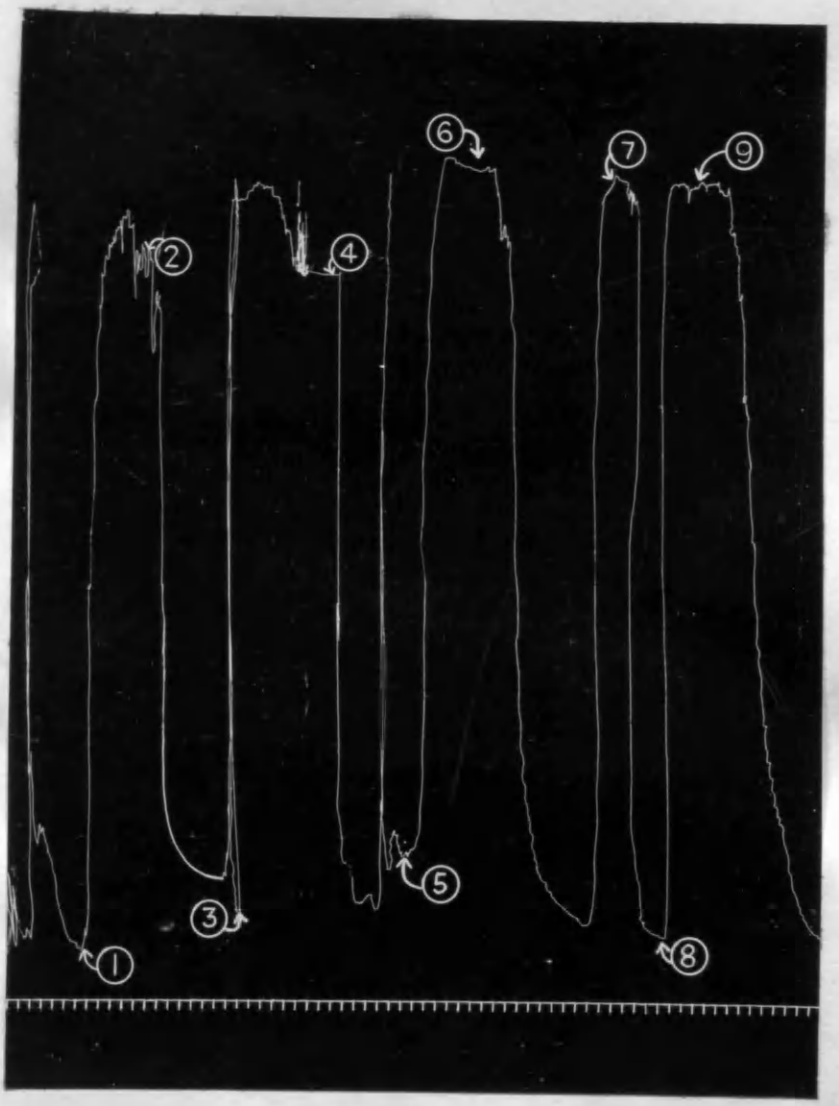

FIG. 73.

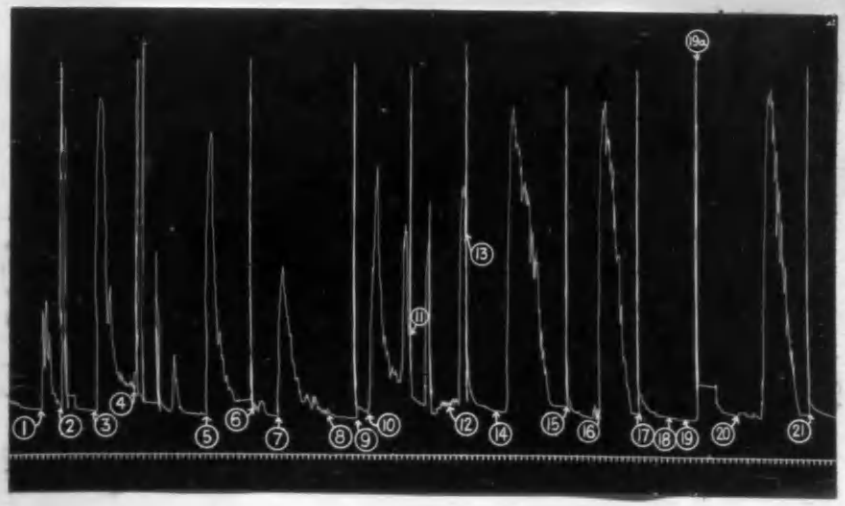

FIG. 74.

Fig. 75.

Small intestine of a cat in the bath.
(1) 1 cc. of brain extract added.
(2) Bath washed out.
(3) 1 cc. of brain extract, after treatment with Norit, added.
(4) Bath washed out.
(5) 0.000156 gm. acetyl choline added.
(6) Bath washed out.
(7) 0.000156 gm. acetyl choline, after treatment with Norit, added.
(8) Bath washed out.
(9) 2 cc. of brain extract added.
(10) Bath washed out.
(11) 2 cc. of brain extract, after treatment with Norit, added.
(12) Bath washed out.
(13) 0.5 mg.atropine sulphate added.
(14) 1 cc. of brain extract, after treatment with Norit, added.

Fig. 76.

Small intestine of a kitten in the bath.
(1) 1cc. of a 1 in 100,000 solu-:tion of histamine added.
(2) Bath washed out.
(3) 0.25 cc. of acetyl choline (1 cc. = 0.006 gm.) added.
(4) Bath washed out.
(5) 1 cc. of brain extract added.
(6) Bath washed out.
(7) 1 cc. of brain extract,after treatment with Norit, added.
(8) Bath washed out.
(9) 0.25 cc. of acetyl choline, after treatment with Norit, added.
(10) Bath washed out.
(11) 0.3 cc. of 1 in 1,000 solution of atropine sulphate added.
(12) 1 cc. of brain extract, after treatment with Norit, added.
(13) Bath washed out.

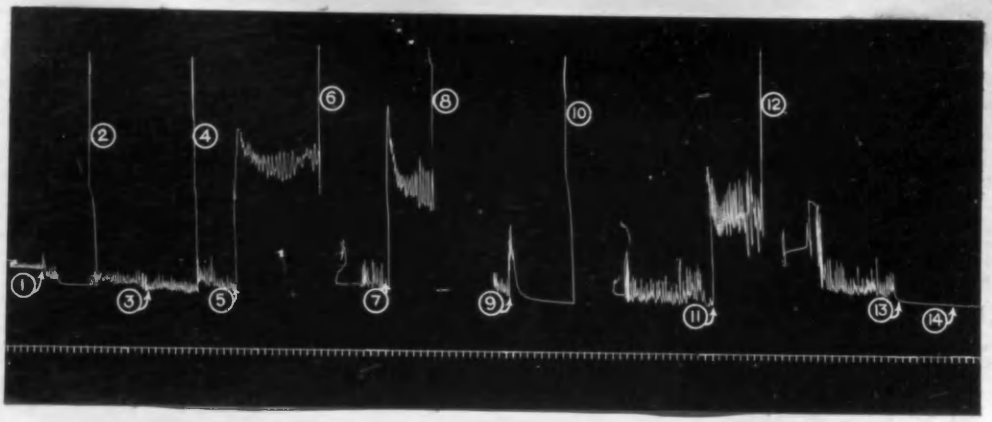

FIG. 75.

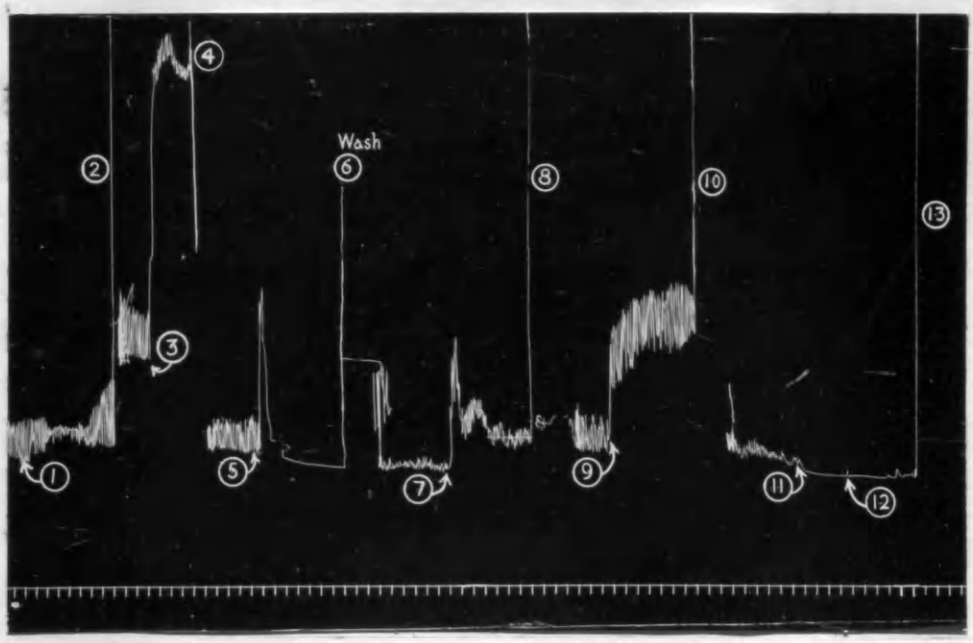

FIG. 76.

Fig. 77.

Small intestine of a cat in the bath.
(1) 1 cc. of 1 in 1,000 solution of histamine added.
(2) Bath washed out.
(3) 0.008 gm. acetyl choline added.
(4) Bath washed out.
(5) 2 cc. of brain extract added.
(6) Bath washed out.
(7) 1 cc. of 1 in 1,000 solution of histamine and 0.0004 gm. acetyl choline added.
(8) Bath washed out.
(9) 2 cc. of brain extract, after treatment with Norit added.
(10) Bath washed out.
(11) 1 cc. of 1 in 1,000 solution of atropine sulphate added.
(12) 1 cc. of brain extract, after treatment with Norit, added.

Fig. 78.

Small intestine of a cat in the bath.
(1) 0.5 cc. of 1 in 100,000 solu-:tion of histamine added.
(2) Bath washed out.
(3) 0.004 gm. acetyl choline added.
(4) Bath washed out.
(5) 2 cc. of brain extract added.
(6) Bath washed out.
(7) 0.5 cc. of 1 in 100,000 solu-:tion of histamine and 0.004 gm. acetyl choline added.
(8) Bath washed out.
(9) 2 cc. of brain extract, after treatment with Norit, added.
(10) Bath washed out.
(11) 0.1 cc. of 1 in 1,000 solution of atropine sulphate added.
(12) 2 cc. of brain extract, after treatment with Norit, added.
(13) Bath washed out.
(14) 0.3 cc. of atropine sulphate added.
(15) 0.0004 gm.of acetyl choline added.
(16) Bath washed out.
(17) 1/100,000 gm. eserine salicylate added.
(18) 2 cc. of brain extract, after treatment with Norit, added.

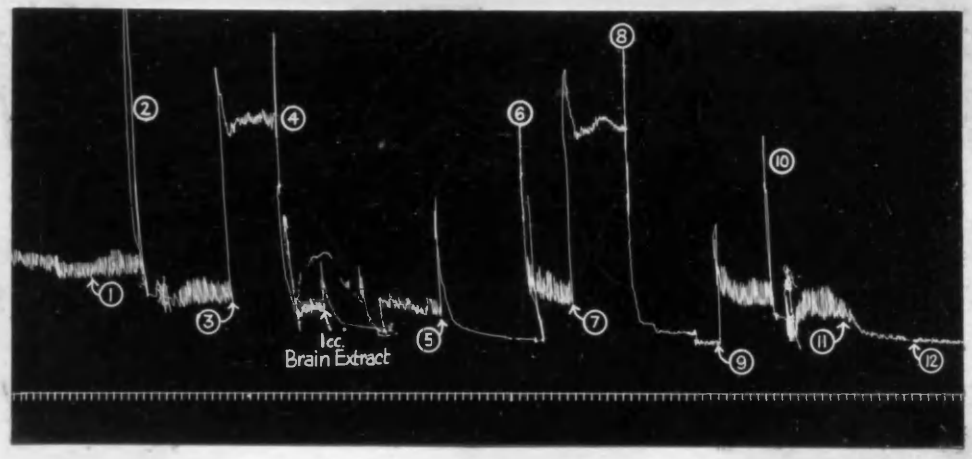
1
2
3
4
1cc.
Brain Extract
5
6
7
8
9
10
11
12

FIG. 77.

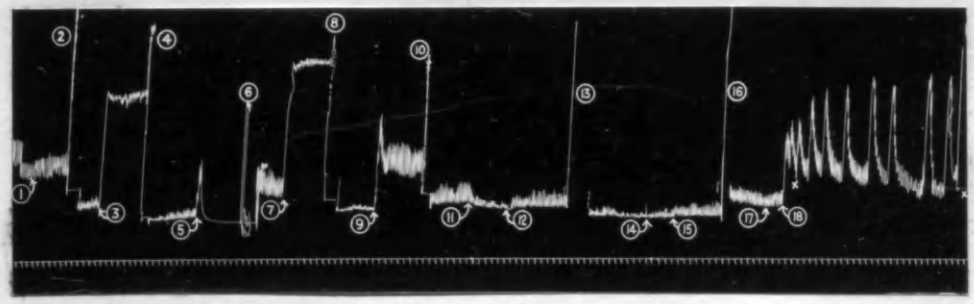
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18

FIG. 78.

Fig. 79.

Record from a cat weighing 3.5 K.

A. Intravenous injection of 3 cc. of brain extract.

B. The same dose injected, after treatment with Norit.

C. Intravenous injection of 0.3 cc. acetyl choline (1 cc. = 0.006 gm.)

D. Intravenous injection of the same dose of acetyl choline, after treatment with Norit.

Fig. 80.

Record from a cat weighing 3.5 K.

A. Intravenous injection of 0.3 cc. of acetyl choline, and 0.5 mg. of atropine sulphate.

B. Intravenous injection of 0.3 cc. of brain extract, after treatment with Norit, and 0.5 mg. of atropine.

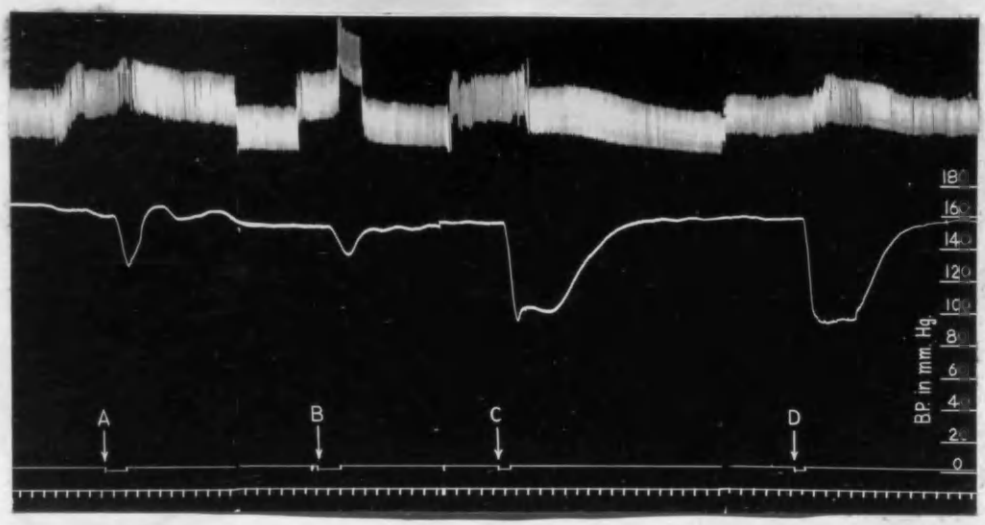
A
B
C
D
BP. in mm. Hg.
18
16
14
12
10
8
6
4
2
0

Fig. 79.

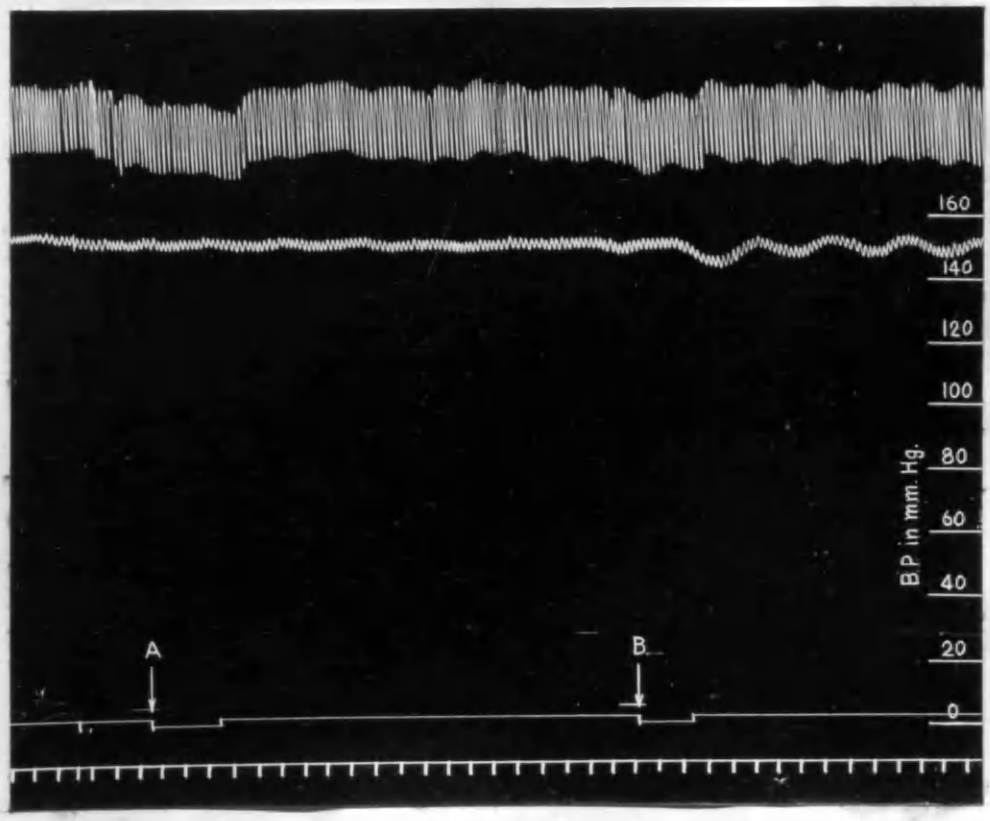
A
B
B.P. in mm. Hg.
160
140
120
100
80
60
40
20
0

Fig. 80.

Fig. 81.

Record from a cat weighing 2.3 K.

A. Intravenous injection of 0.2 cc. acetyl choline (1 cc. = 0.0006 gm.)

B. Intravenous injection of same dose, after treatment with Norit.

Fig. 82.

Record from a cat weighing 2.4 K.

A. Intravenous injection of brain extract after treatment with Norit, and the addition of 2N NaOH.

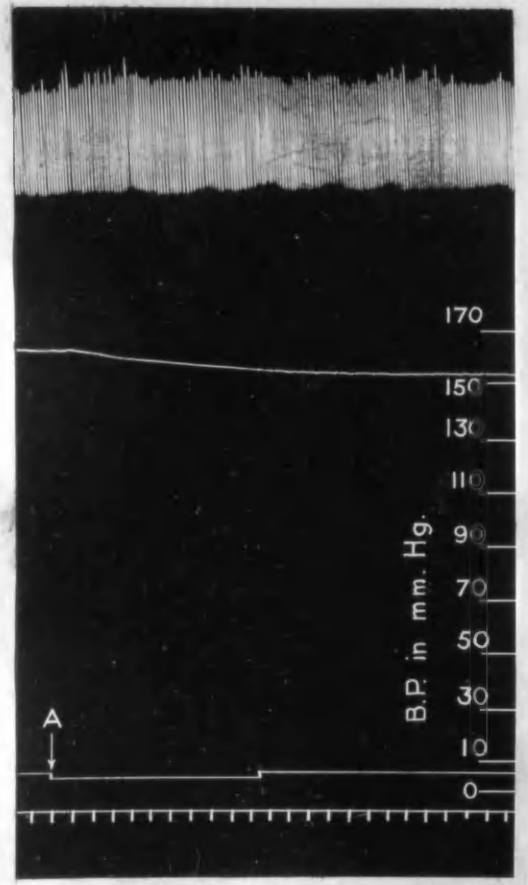
170
150
130
110
90
70
50
30
10
0
B.P. in mm. Hg.
A

Fig. 82.

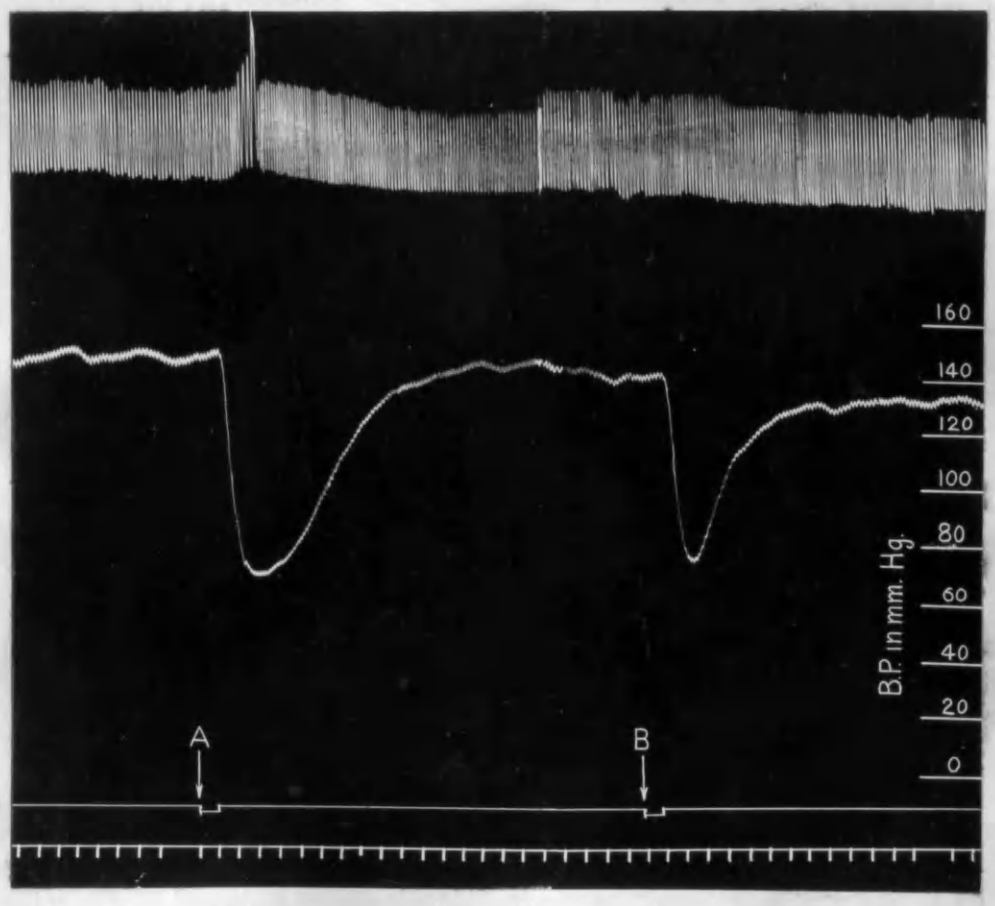
160
140
120
100
80
60
40
20
0
B.P. in mm. Hg.
A
B

Fig. 81.

Fig. 83.

A. Intravenous injection of a dilute dose of brain extract, after treatment with Norit.

Fig. 84.

A. Intravenous injection of brain extract, after treatment with Norit, along with the animal's whole blood.

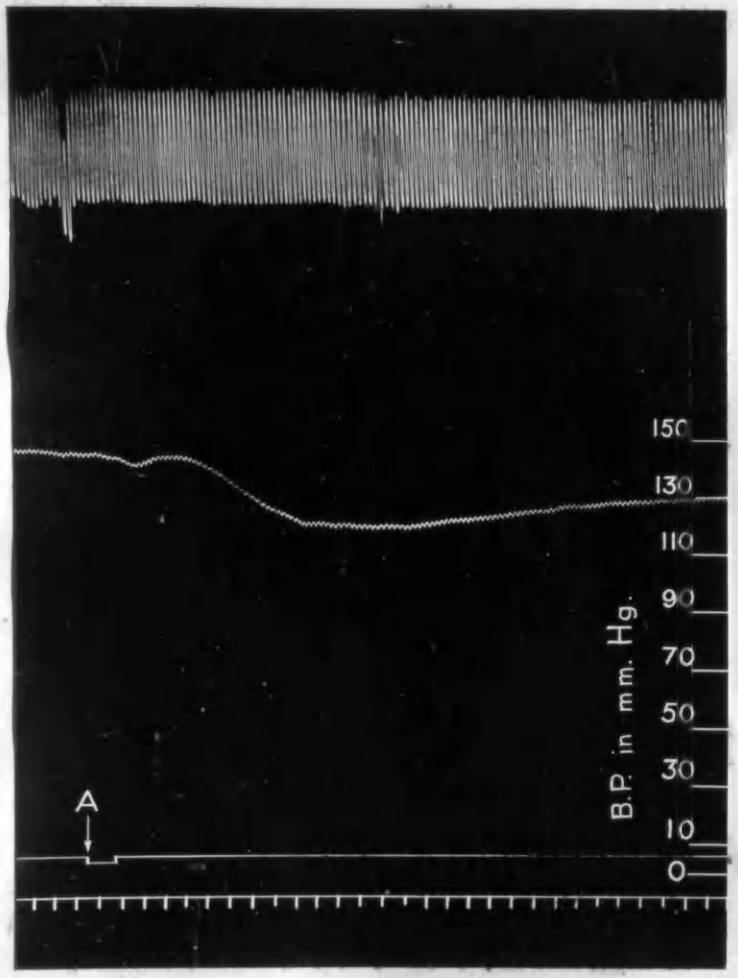
150
130
110
90
70
50
30
10
0
B.P. in mm. Hg.
A

Fig. 84.

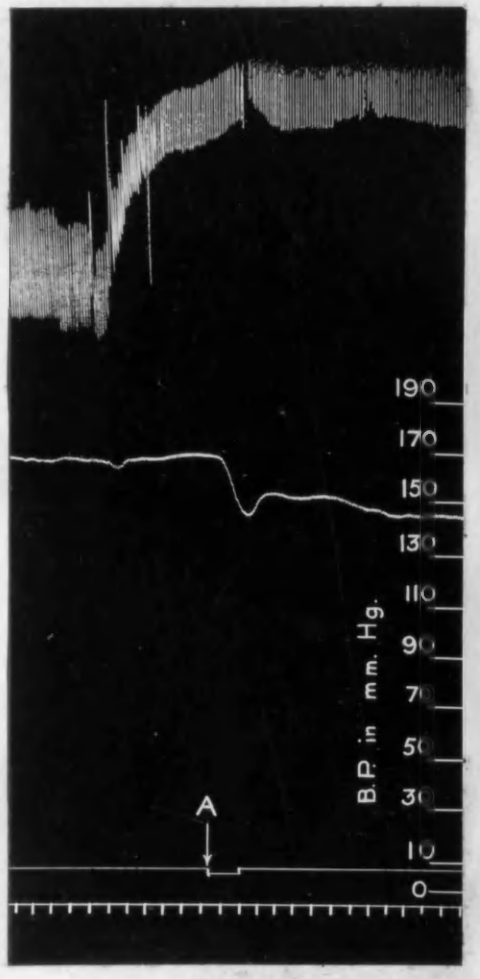
190
170
150
130
110
90
70
50
30
10
0
B.P. in mm. Hg.
A

Fig. 83.

Fig. 85.

A. Intravenous injection of 0.3 mg. of eserine salicylate.

Fig. 86.

In this case, the animal had previously been given eserine salicylate.

A. Intravenous injection of 0.3 cc. of brain extract, after treatment with Norit.

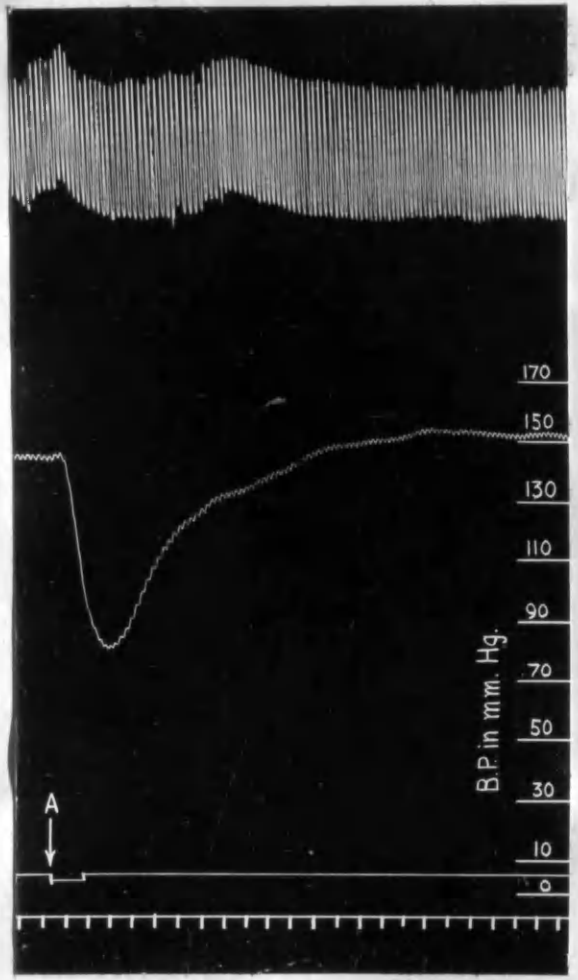
170
150
130
110
90
70
50
30
10
0
B.P. in mm. Hg.
A

FIG. 86.

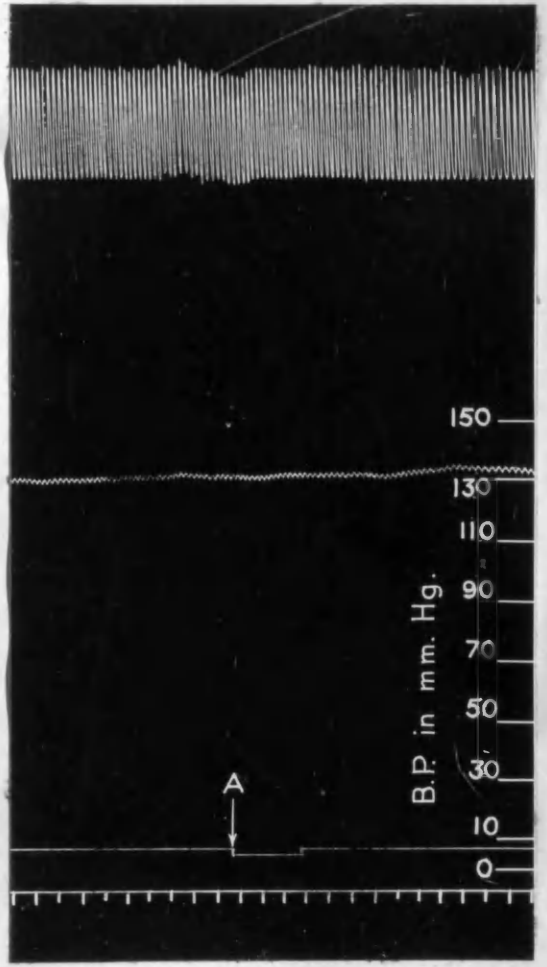
150
130
110
90
70
50
30
10
0
B.P. in mm. Hg.
A

FIG. 85.

Fig. 87.

A. Intravenous injection of one drop of 0.01 gm. acetyl choline in 3 cc. of the animal's own blood.

B. Artificial respiration.

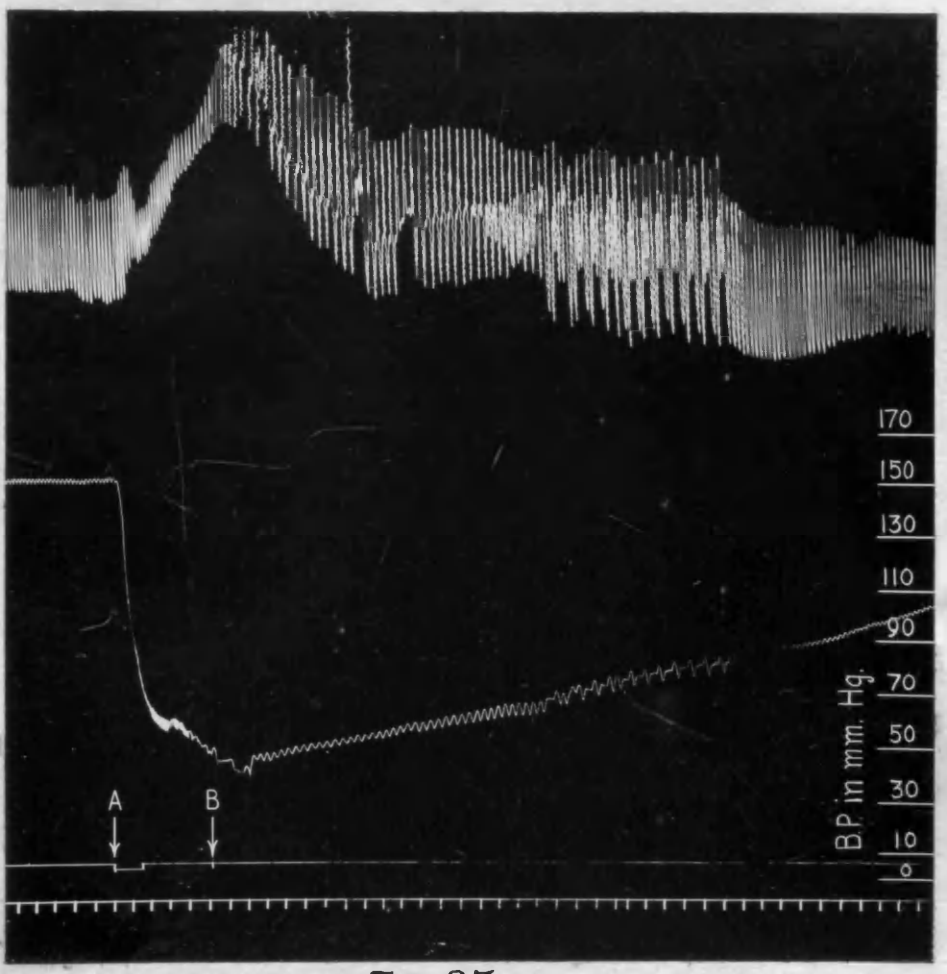

Fig. 87.