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ON THE REGULATION OF THE BLOOD-SUPPLY OF THE BRAIN.

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Plates II., III. and IV.

From the Cambridge Pathological Laboratory.

One marked characteristic of the literature dealing with the cerebral circulation is, we think, the contradictory nature of the results which have been obtained by different investigators.

There is no reason, we imagine, for doubting that the cause of these discrepancies is to be found in the great difficulty of avoiding the sources of error which plentifully surround the subject, and in overcoming certain technical difficulties which we shall presently have to refer to. The ease with which one can obtain results upon certain points, on taking up the subject, is itself, we believe, apt to make the inquirer careless in controlling sources of error, which, it may be noted, are some of them not at first sight obvious. We must on this account say more about the technology of our subject than would be necessary were the subject a simpler one.

Methods employed by other observers.

In order that the bearing of our method may be understood, we think it well to refer to some of the other modes by which different observers have investigated the cerebral circulation. Some observers have simply inspected the exposed pia mater, as was done by Haller[1]. In most, if not all, of these experiments there appears to have been no simultaneous record taken of the arterial or venous pressure. That such a method, so rough in itself, could easily lead to untrustworthy results—giving as it does no means of distinguishing active changes in calibre of the cerebral vessels from passive variations of their width produced by changes in the arterial and venous pressures—will, we think, be readily admitted.

[1] *Opera Minora.* Tom. I. p. 131.

Measurement of the outflow from one of the cerebral veins[1] is, in many respects, a considerable improvement on the mode by simple inspection. It is not, however, an easy thing to obtain graphic records of the venous out-flow from the brain which can be compared with graphic records of the arterial pressure. Owing to this and other inherent difficulties, the method has, as yet, been but scantily employed.

The method used by Francois-Franck[2] and Hürthle[3], of measuring simultaneously the pressures in one of the systemic arteries and in the cerebral end of the cut internal carotid is, we think, by no means free from serious sources of error. The freedom of anastomosis between the vessels forming the circle of Willis cannot, we are of opinion, be assumed to bear any constant relation to the degree of expansion of the vessels supplying the brain-substance. We may also add that we do not gather from the papers in question that adequate precautions were taken to control mistakes arising from changes in the general venous pressure.

A fourth method, with which valuable work has been done by Mosso[4] and others, can be employed in man in cases where there is a defect of some part of the cranial vault. Such apertures being usually closed by a more or less elastic fibrous membrane, it is possible to see, feel, and, if desired, to record graphically the changes in volume of the cranial contents which result from variations in the amount of blood present within the intracranial vessels. Much of our knowledge regarding some of the characteristics of the cerebral circulation has been obtained by this method, which is well fitted to give information with regard to certain points. By it can be learned some of the conditions which cause cerebral congestion, and certain of those which produce cerebral anæmia. We can also study the form of the pulse-curve which results from changes in the pressure of the cerebro-spinal fluid after each heart-beat. We cannot, however, in man measure the pressure either in the systemic arteries or in the veins, so that we cannot tell whether any of the changes in the volume of the brain are or are not due to active changes in the calibre of the cerebral blood-vessels. Nor can we in man make such experiments as involve the section or stimulation of nerves, or observe the effects on the cerebral

[1] Gaertner u. Wagner, *Wien. Med. Wochensch.* 1887. No. 19 and 20.
[2] *Sur les Fonctions Motrices du Cerveau*, p. 199. Paris, 1887.
[3] "Beiträge zur Haemodynamik." *Pflüger's Arch.* Bd. XLIV. S. 561.
[4] *Ueber den Kreislauf d. Blutes im Menschlichen Gehirn.* Leipzig, 1881.

blood-supply of poisons or of certain remedies which are used in medicine.

These objections do not apply in the case of observations made on the lower animals with an artificial opening through the skull and dura mater. Simple and satisfactory as this latter method may seem at first sight, there are certain technical difficulties connected with it which presumably is the reason why it has been adopted by only a small number of observers. Further, it appears that, so far as we can learn, all those who have applied this method have employed it to study variations of intracranial pressure merely, the junction between the recording instrument and the cranial cavity being watertight, so that the record obtained is influenced to an enormous extent by passive changes in calibre of the large arteries and veins. We incline to believe that the observers who have used this method have not sufficiently recognised the necessity of taking, simultaneously with the curve from the cranial cavity, graphic records both of the arterial and venous pressures. The influence of changes in these latter where this method is employed, is so great that results obtained without due control of them must, we think, be looked upon as likely to mislead. A practical objection which has stood in the way of the employment of the method is that the brain, the volume of which can be greatly increased by a variety of causes, may, by protruding through the trepan hole, more or less completely plug it, thereby preventing further records being taken.

Method employed by us.

Our observations were made chiefly on dogs, although many of our results were controlled by repeating the experiment on cats or rabbits. The animals were in most cases under the influence of curare in addition to an anæsthetic.

A trepan hole—about 22 mm. in diameter in the case of dogs, but smaller when a cat or a rabbit was used—was made as near the middle line of the vertex of the cranium as is compatible with avoidance of the longitudinal sinus, after which the subjacent dura was removed by a circular incision.

After any oozing of blood from the diploe had ceased, a small metal capsule, of a size corresponding with that of the trepan hole, was fixed over the aperture by means of screws. The shape of the capsule, and the mode of fixing it firmly to the skull can be seen on reference to Fig. 1. Pl. II.

The lower opening of the bell-shaped capsule (*a*) is closed by a very

flexible, delicate, animal membrane[1] (*e*), of the kind already used by one of us (R.) in other apparatus. It is tied on in such a way that it readily follows all changes in the level of the part of the cortex on which it rests, while it prevents any escape of the air with which the capsule is filled. Outside the capsule, about two mm. from its lower edge, is a projecting rim (*b*), which rests on the external surface of the cranial bone. This rim has in it two notches, in which fit two metal pins (*c* and *d*), bent at right angles at their lower ends, so that they can hook under the bone on opposite sides of the hole. By means of small thumb-screws on the upper parts of these pins, the capsule is held firmly in position. The upper opening of the capsule is connected by means of rigid-walled tubing with the recording apparatus. This latter consists of an arrangement similar to that which one of us has described[2] as useful for studying the form of the pulse-wave and which is shewn in Fig. 1*a*, Pl. II. A light piston, escape of fluid by the side of which is prevented by a flexible membrane of the kind already referred to, conveys to a recording lever any changes in the volume of the brain. In order to prevent the cortex protruding and thus plugging the trepan hole, pressure on the brain of any desired force can be exerted by means of a delicate thread of india-rubber which presses down the piston.

This object can, we find, however, be still better attained, by hanging a small weight (one gramme) on the lever at any desired distance from its axis. By this means it is easy to keep the volume of the brain within appropriate limits. When the brain tends to expand too much, the weight is placed nearer the writing point of the lever, when, on the other hand, the tendency to contraction passes the desired limit, the weight is placed nearer the axis or beyond it, so as to reduce sufficiently the weight of both lever and piston.

As we did not desire to study the form of the pulse-curve obtainable from the contents of the cranial cavity, the increase of inertia resulting from the employment of the small weight does not invalidate the trustworthiness of the record obtained in regard to those points on which we wished to obtain information from it.

We have carefully avoided any risk of the graphic record of changes in the volume of the cerebral hemisphere being affected by alterations in the pressure of the cerebro-spinal fluid. The cerebro-spinal fluid was permitted to escape freely from the cranial cavity by the side

[1] *Obtainable from the Cambridge Scientific Instrument Company.*

[2] Roy. This *Journal*, Vol. III.

of the metal capsule. In the few cases where we saw reason to suspect any obstruction to the free escape of this fluid, one or more deep notches were made with "parrot bill" bone-forceps in the edge of the trepan hole, in order to be certain of eliminating the influence of pressure changes in this fluid. Our apparatus is, therefore, intended to register the variations of vertical thickness of the cerebral hemisphere. It was early found advisable to magnify the graphic record much less than has been done by those who have worked upon the intra-cranial pulse-wave. As can be seen by reference to our tracings, the pulse is never magnified more than just sufficiently to indicate the individual waves. All the results recorded in the following pages were obtained from experiments in which the arterial pressure in one of the femorals was recorded at the same time as the oncographic tracing of the brain was taken.

We have, further, controlled all results on which, in the following pages, any weight is laid by observing the venous pressure in one of the jugulars, in which was inserted a T tube connected with a manometer containing sodium bicarbonate solution. We are now convinced that, in observations on the cerebral circulation, it is essential to measure, during the experiment, both the arterial and the jugular pressures. Had this been done by previous observers, we are of opinion that the literature of the subject would not contain so many discrepancies.

I. Effects of Stimulation of Sensory Nerves.

(Figs. 2, 3, 7, 8.)

Stimulation by induced currents of the uncut, or of the central end of the cut, sciatic nerve always, in our experiments, produced expansion of the brain. The expansion begins almost immediately after the commencement of the stimulation, and lasts a varying number of seconds after the latter has ceased. The volume of the brain then returns to what it was before the application of the stimulus. A similar effect on the volume of the brain results from stimulation of any other sensory nerve. Amongst other nerve-trunks stimulated for this purpose we may mention the ulnar, lingual, musculo-cutaneous, splanchnic and vago-sympathetic. Stimulation of the skin or conjunctiva has a similar effect on the vessels of the brain.

As to the nature of this expansion, it is found to go more or less hand in hand with that rise of pressure in the systemic arteries which results from stimulation of sensory nerves.

Figs. 2 and 3, Pl. II. may be referred to as typical examples of the general correspondence between the brain-curve and that of the blood-pressure in the aorta.

In Fig. 2, shewing the effect of electric stimulation by the induced current of the central end of the cut sciatic nerve, it can be seen that the summit of the wave of cerebral expansion is flatter than that of the corresponding wave of increased arterial pressure. This characteristic is to be seen also in Figs. 7 and 8, Pl. III., and, indeed, is usually to be found in our curves of passive arterial congestion of the brain. It is presumably due to the friction within the small arteries, capillaries, and veins of the brain retarding the escape of blood from the organ and preventing the decrease in volume of the hemisphere from accompanying exactly the fall of the arterial pressure. In the case of Fig. 3, there is a less exact correspondence between the volumetric brain-curve and the tracing of the arterial blood-pressure. That this want of fairly complete conformity between the curves in Fig. 3, as well as in other similar cases, is due to changes in the venous pressure is not we find very easy to prove or to disprove. We do not feel prepared to say more than that according to our observations, the increase in the volume of the brain which results from stimulation of sensory nerves is mainly if not entirely due to passive or elastic distension of its vessels as a result of the rise of blood-pressure in the systemic arteries.

It may be added that the increase in volume of the brain which is produced in this way is relatively much greater than that met with in cases of passive arterial congestion of the kidney for example, which, of course, is only what might *a priori* be expected, when it is remembered how thin-walled are the cerebral vessels compared with the vessels of other organs and tissues.

II. Effects of interference with the inflow or outflow of blood from the Cranium.

Closure of both carotids causes, as might be expected, enormous contraction of the brain. Closure of one carotid did not, in any of our experiments, produce an appreciable effect on the volume of the organ, nor did the closure of one jugular vein affect the volume appreciably.

Closure of both external jugulars, either by ligature of these veins, or by tightening a cord round the neck, so as to close the veins without hindering the flow through the arteries, causes excessive expansion of

the brain. It must, therefore, be kept in mind that the pressure in the veins influences readily the volume of the brain.

Lowering of the arterial pressure from loss of blood or other cause, is accompanied by a diminution in the volume of the brain. The cerebral anæmia so produced follows so closely the blood-pressure curve that it must be looked upon as resulting entirely from passive contraction of the elastic walls of the cerebral vessels.

III. Asphyxia.

Stoppage of the artificial respiration, in cases where that is being employed in curarized animals, causes a great expansion of the brain. This expansion occurs at a varying time after the respiration has been stopped, and it commences more or less simultaneously with the rise of arterial pressure which usually results from asphyxia.

The curves of Figs. 4 and 5, Pl. II., shew, however, that although the oncographic and the blood-pressure curves may rise more or less simultaneously, they by no means correspond to one another in their later course.

In Fig. 4 the expansion of the brain continues for a few minutes after the blood-pressure has fallen to the level which it shewed before the respiration was stopped.

In Fig. 5, on the other hand, there is less correspondence between the expansion of the brain and the arterial pressure, which latter rises but very little as a result of the arrest of the respiration.

These curves shew that the heightened arterial pressure in asphyxia, although it necessarily assists in expanding the brain, cannot be looked upon as the only factor. In considering the question whether this asphyxial congestion of the brain be an active or a passive one it is mainly the possibility of the volume of the brain being affected by changes in the venous pressure which must be considered. If the changes in the pressure in one of the jugulars be measured during the asphyxial condition it will be found that, in most cases, no increase of pressure in the veins takes place. On the contrary, during the earlier stages of asphyxia, with which alone we are at present concerned, there is usually a fall of the venous pressure as can be seen in Fig. 6, Pl. II. In that curve is shewn the usual effect of asphyxia on the venous pressure which was recorded simultaneously with the pressure in one of the femorals.

On comparing the venous and arterial pressures with the oncographic curve we find, then, that there is no rise of venous pressure such as

might explain the expansion of the cerebral vessels, and that, by no means infrequently, the venous as well as the arterial pressure has returned to that which it presented before the respiration was stopped, while the brain remains for a varying number of minutes more expanded than before.

It must, therefore, be admitted that during asphyxia active expansion of the cerebral vessels takes place in addition to the passive distension which results from the rise of the arterial, and in certain instances, of the venous pressure. We shall have occasion to refer to the possible explanation of the active expansion of the cerebral vessels during asphyxia when we are considering the effect on the cerebral circulation of interference with the nutrition of the brain.

IV. Effect of direct Stimulation of the Medulla Oblongata.

Direct stimulation by the induced current of the medulla oblongata, in curarized animals, causes congestion of the brain. This congestion, as in the case of certain others already referred to, is passive (arterial), going hand in hand, as it does, with the rise of arterial pressure which results from the narrowing of the vessels of other organs and tissues of the body. Induced currents passed through the spinal cord at various parts of its length have an effect upon the brain similar to that produced by stimulation of the medulla.

We have been unable to convince ourselves that there is any accompanying active expansion of the cerebral vessels. The curves obtained resemble those produced when the central end of a sensory nerve is stimulated.

V. "Traube-Hering" Curves.

In Fig. 4, Pl. III., can be seen the changes in volume of the brain which occur when the vaso-motor centre causes the rhythmic variations of the blood-pressure which are generally called "Traube-Hering" waves. When these undulations appear during an experiment on the cerebral circulation (and in our experience they are especially frequently met with in such experiments), the brain expands with each rise of the blood-pressure and contracts with each successive fall, as is well shewn in Fig. 4, where it can also be seen that the oncograph waves are more rounded at their summits than are the corresponding blood-pressure waves—a point which we have already referred to.

VI. Effect of Muscular Movements.

If the animal struggle while under the influence of a weak dose of curare, or when it is under either chloroform or morphia alone, the muscular movements are accompanied by cerebral congestion which may be very considerable in extent. The congestion appears, in this case also, to result mainly, if not exclusively, from the rise of pressure in the arteries and veins. The curve of volume of the brain resembles in its general characters that of the arterial pressure, although the rise of the venous pressure must assist in expanding the cerebral vessels. The more generalized and powerful the muscular movements are the greater is the concomitant congestion of the brain. As in the case of stimulation of sensory nerves, we cannot be certain that the cerebral congestion is not due in some degree to active expansion of certain of the cerebral vessels, although certainly the main cause is the rise of pressure in the arteries and veins.

VII. Vagus of Rabbit. Vago-sympathetic and splanchnic of the Dog.

In the rabbit, stimulation of the uncut vagus caused diminution of the volume of the brain in the two experiments in which we tried it. This contraction appeared to be due to the fall of blood-pressure which usually results from excitation of the vagus in that animal.

The literature of the cerebral circulation contains accounts of curiously discrepant results which have been obtained as a result of section or stimulation of the vago-sympathetic in the dog or of the corresponding nerves of the cat or rabbit. It has given us much food for reflection to compare our own results with those of other observers, keeping in mind in each case the method which had been employed[1].

A glance at Figs. 7, 8, and 9, Pl. III. will shew that the effects on the volume of the brain of stimulation of the vago-sympathetic, whether of the undivided nerve or of its upper cut end (the corresponding nerve of the other side being intact) may be, at first sight, sufficiently contradictory.

In Fig. 7 can be seen two of the effects of stimulation by the induced current of the central end of the divided vago-sympathetic nerve of one side. The cut nerve was thrice stimulated, the same strength of current being employed in each case. On the first stimulation the blood-

[1] A *résumé* of most of the German observations on this subject is given in Hürthle's paper, l.c., S. 578.

pressure rose, the brain expanding with the rise, and contracting with the fall, of the arterial pressure. As a final result however the brain was left less expanded than it was before the stimulation.

On repeating the stimulation about a minute later, the brain at once began to expand, the oncograph tracing ascending until, in about another minute, the lever point had nearly reached the upper edge of the paper, which level however was as high as it was possible for it to reach. Be it noted in passing that this second stimulation did not cause more than a comparatively slight rise of the arterial pressure. A third stimulation increased the rapidity of the expansion of the cerebral vessels, although this increased rapidity of expansion is accompanied by a considerable rise of the arterial pressure-curve and is therefore presumably due to passive arterial congestion.

Fig. 8 shews two other instances from another dog of the effect of stimulating the central end of the cut left vago-sympathetic, the corresponding nerve of the other side being intact as in the case of Fig. 7. Here, again, the interrupted currents were of the same strength in both stimulations. With the first excitation, the brain expanded with the rise of arterial pressure, afterwards decreasing "*pari passu*" with it for a certain time. It continued, however, to diminish until the lever point fell below the drum, although there was no corresponding fall of the kymographic tracing.

As the brain remained contracted, the drum was stopped for a moment and the lever point raised by moving the weight to another point on its length, so as to lessen the pressure on the brain.

On repeating the stimulation the oncographic curve rose and fell with the rise and fall of the kymographic tracing which it followed very fairly exactly, although the brain at the end remained more expanded than it had been immediately before the second excitation of the nerve.

In the first part of Fig. 9 is shewn one of the effects of electric excitation of the uncut vago-sympathetic. As can be seen, the result in this case was a great expansion of the brain which accompanied an actual fall of the arterial pressure.

The above described results, which were to us at first sight very confusing, cannot all of them be produced at will in the case of any given animal. The mere fact, however, that effects so contradictory in appearance can be produced by stimulation of the nerve in question, leaves small room for wonder that the results of previous observers should have differed so much from one another as they do—

why some have found vaso-constrictors for the brain and some vaso-dilators for that organ in the cervical sympathetic or vago-sympathetic, while some found that this nerve had no direct influence on the cerebral vessels.

The results of section of one or both of these nerves may, we found, produce in one experiment anæmia of the brain, in a second congestion, while, in a third, no noticeable effect on the brain is produced. In cases where a positive result follows section of these nerves, it is not accompanied by any such change in the arterial pressure as could be supposed to be the cause of it. This want of conformity between the oncographic and kymographic tracings is illustrated by Fig. 10, Pl. IV., which shews expansion of the cerebral vessels resulting from the section, first of one and then of the other, of the two vago-sympathetics.

Of course, with such extraordinary results of section and stimulation of the nerves in question, as are illustrated by the Figs. 7, 8, 9 and 10, and which we have just attempted to describe, it was impossible for us at first to avoid the feeling that we were a very long way indeed from a true comprehension of the matter.

We thought that escape of current from our electrodes might perhaps explain the mystery, and sought to control that source of error by stimulating the carotid sheath as well as by excitation of the smaller nerves of the front of the neck. We even applied an induced current to the thyroid gland! At length, and somewhat with a feeling of despair, we tried stimulation of the lower end of the cut vago-sympathetic with results, one of which is illustrated in the second half of Fig. 9.

This tracing shews, that when the cardiac end of the cut vago-sympathetic is excited, there may be marked expansion of the cerebral vessels accompanying a diminution of the medium blood-pressure in the arteries. On learning this fact, it gradually dawned upon us that we had been looking at the matter upside down; in other words that the above described results, which were of so puzzling a kind when one sought to explain them as due to the action of ascending fibres in the vago-sympathetic might be much more easy of interpretation, if we tried to find how far they could be explained by some action of descending fibres in the nerves in question.

A brief inquiry in this latter direction put the matter on a very simple footing indeed, in so far at all events, as the cerebral circulation is concerned. We found, namely, that in the vago-sympathetic there exist descending fibres capable of influencing powerfully the general venous pressure, and that direct stimulation of the lower end of the cut

nerve may cause either rise or fall of the pressure in the great veins entering the thorax.

We found, also, that the same twofold effect may be called forth by reflex stimulation of these nerves, *i.e.* by exciting the upper end of one cut nerve while the corresponding nerve of the other side is intact, and that this reflex ceases when both nerves are cut. Where both vago-sympathetics have been cut, electric stimulation of the cerebral end of one of them produces results similar to those produced by excitation of other sensory nerves.

We found, by direct observation, that we could not obtain any of the well-marked effects on the cerebral circulation of stimulation of the vago-sympathetic, which are illustrated by our curves, without the production at the same time of a change in the intra-venous pressure corresponding closely to the former in direction and extent. We can see therefore no room for doubting that the changes in the volume of the brain which are produced by stimulation or section of the vago-sympathetic nerves, are passive in nature, and can be explained by changes in the pressure of the blood within the veins.

A rise of the venous pressure equal to 3 or 4 inches of water-pressure, is of no uncommon occurrence as a result of stimulation of the lower end of the cut vago-sympathetic. On the other hand a fall of pressure in the jugulars cannot of course lead to the pressure in them becoming subatmospheric.

As to the mechanism by which these changes in venous pressure are produced they might, we presume, be due to vasomotor fibres acting directly on the muscular coat of the veins, or affecting the freedom with which the blood enters or leaves the veins. This is a matter which we cannot go into here and we only note in passing that, according to our observations, there are in the vago-sympathetic nerves descending fibres, section or stimulation of which can produce either a rise or a fall of the general venous pressure, and that these fibres can be called into action either by direct stimulation, or reflexly, by excitation of ascending fibres, the corresponding nerve of the other side being intact.

Stimulation of the splanchnic nerves caused, in the two instances in which we tried its effect, changes in the volume of the brain which were so completely in accordance with the arterial pressure-curve that there was no doubt that the changes were due to passive arterial congestion.

VIII. Effects of drugs on the cerebral circulation.

1. Chloral Hydrate.

Chloral produces marked contraction of the brain which is not accompanied by any corresponding fall in the arterial pressure. In one instance, this cerebral anæmia was preceded by a temporary congestion lasting two or three minutes. In all of our experiments on this subject, the diminution in volume resulting from the administration of chloral (in medicinal doses) was gradual, and continued for a considerable time after the injection of the solution into the vein. We have made no observations on the question as to whether or not the venous pressure is altered by chloral.

2. Chloroform.

When administered in the usual way by inhalation, chloroform causes marked contraction of the brain which is only in part due, so far as we have observed, to the fall of the arterial pressure. In one of our experiments, no appreciable change in the volume of the brain resulted from inhalation of chloroform.

3. Sulphuric Ether.

When injected into a vein, Sulphuric Ether in medicinal doses causes great expansion of the brain which is probably due to the rise of venous pressure which is likewise produced. When inhaled, primary contraction, lasting for a varying time, is followed by well-marked expansion.

4. Morphia.

Medicinal doses of morphia caused, when injected into a vein, contraction of the brain, but this, in our few experiments on the subject, was found to be slight in extent, though somewhat lasting. Tincture of opium produced, in some cases, primary contraction of the cerebral vessels which lasted for some time. In other instances, a primary expansion of the brain passed over into a secondary contraction; whilst in others there was primary expansion of the cerebral vessels which lasted till the animal experimented upon was killed. This was the case in the experiment which is illustrated by Fig. 12, Pl. IV. We do not know how far any changes in the venous pressure are responsible for these effects. They are not the results of changes in the arterial pressure. Contraction, i.e. anæmia of the brain, was on the whole the most constant and marked effect of the intra-venous injection of medicinal doses of opium.

5. Bromide of Potassium.

Intra-venous injection of a solution of Potassium Bromide, in medicinal doses, causes expansion of the brain, this expansion having been preceded in two instances by temporary contraction of the organ.

6. Strychnia.

Injection into a vein of a sub-lethal dose of Liquor Strychniæ produces enormous expansion of the brain. Even with small doses the congestion of the cerebral vessels is very great. Our curves shew no primary contraction of the brain,—the rise commencing in a minute or a little more, after the injection of the drug, and rapidly carrying the lever point beyond the top of the drum, as can be seen in Fig. 11, Pl. IV. We have not been able to determine satisfactorily whether this strychnia congestion is or is not exclusively due to the rise of arterial pressure which is so marked a result of the administration of strychnia. The sudden and great expansion of the brain begins at the same moment of time as the rise of the blood-pressure curve.

Gärtner and Wagner[1], whose method excluded the effect on the cerebral circulation of changes of the venous pressure, found that strychnia produced a very great increase in the amount of blood leaving the transverse sinus, which increase they ascribe entirely to the rise of the arterial pressure. Instead of leaving the transverse sinus drop by drop, as is usually the case, the blood, after administration of strychnia, spirts out in a continuous stream.

7. Caffein.

Caffein when introduced into a vein in medicinal doses, produced in the two instances in which we have tried its effect, a slight primary expansion, then a slight transient contraction followed by a persistent and well-marked expansion, leaving the brain more expanded than before the caffein was injected.

8. Acids and Alkalies.

Of all the substances, whose influence on the cerebral circulation we investigated, none produced results more unexpected than acids and alkalies. The intra-venous injection of free acid—sulphuric or nitric or lactic were the acids chiefly used by us—in small doses freely diluted

[1] Loc. cit.

with ·75% salt sol. and injected slowly, produced, in all our experiments on the subject, great and immediate expansion of the brain. The extent of the congestion resulting from the administration of 1 – 2 minims of Acid. Sulph. or Acid. Nitric. sometimes approaches in intensity that produced by strychnia. In the case of the acid, however, there is no rise of pressure in the systemic arteries sufficient to cause the cerebral congestion by mechanical distension of the thin-walled arteries of the brain and which as already mentioned may account for the strychnia congestion. The congestion resulting from injection into a vein of a moderate dose of acid lasts for some considerable time, the curve rising at first rapidly and then more slowly until a maximum is reached some 5—10 min. after the injection. From this point the tracing descends slowly and continuously but does not fall so low as the position at which the lever stood at the time of the injection.

The effect of alkalies—of which we employed chiefly potassium hydrate—is diminution of the volume of the brain. This anæmia is the primary effect of the injection on the circulation of the brain. The curve descends rapidly immediately after the injection, the lowest part of the tracing occurring some minutes afterwards and the succeeding re-expansion of the brain, which is more and more gradual, does not restore it to the volume it presented before the injection.

These opposite effects of acids and alkalies on the cerebral circulation were constantly met with in all our experiments on this part of our subject.

9. Liquor Ammoniae.

Intravenous injection of medicinal doses of Liq. Ammoniæ produced, in the three instances in which we employed it, well-marked expansion of the brain. In one of these cases the congestion was preceded by a temporary contraction.

10. Quinae Sulphas.

The effect of sulphate of quinine on the cerebral circulation was not found by us so great as to lead to the impression that the cerebral effects of this drug, which can be so unpleasant in man, are to be ascribed to its effects on the cerebral circulation. Our tracings shew that it produced a well-marked temporary fall followed by a lasting slight expansion.

11. Other substances.

On the following our observations have been either isolated, or the results have been so little striking, that we are not prepared to lay any

great weight upon them. *Alcohol*, in moderate doses, caused expansion, but this congestion was not great in extent. *Atropine Sulphate*, in small doses, produced slight congestion. *Hydrocyanic Acid* in lethal dose caused slight temporary contraction of the brain lasting a few minutes. This was followed by great expansion, which gradually passed over into the fall accompanying failure of the heart. *Urea* produced no marked effect. *Tincture of Digitalis* produced expansion of the brain resulting mainly, if not entirely, from the rise of pressure in the systemic arteries.

We may here mention that we do not propose, in the present communication, to refer to the results of our observations on the form of the pulse wave of the brain. Nor do we desire to enter upon the question of the condition of the cerebral circulation during natural sleep.

Conclusions.

We now come to the question as to the interpretations which may, in our opinion, be legitimately drawn from the facts which have been stated on the preceding pages.

What, first of all, is to be gathered from our observations (keeping in mind of course the results obtained by other workers), as to the relation which the cerebral circulation bears to that of the rest of the body? One of the most evident of the facts observed by us is that the blood-supply of the brain varies directly with the blood-pressure in the systemic arteries.

The higher the arterial pressure, the greater is the amount of blood which passes through the cerebral blood-vessels and *vice versâ*; and, so far as we have been able to learn, this law holds good for all changes in the arterial pressure whatever be their cause. The same may be said regarding the blood-supply of other organs of the body if their connec- regarding the blood-supply of other organs of the body if their connections with the vasomotor centres have been severed; but it applies very much less to the kidney, for example, after complete section of the renal nerves, than it does in the case of the brain. The thinness and extensibility of the walls of the cerebral vessels fit them to undergo much greater variations in calibre as a result of a given rise or fall of the arterial pressure than can be produced in the case of the thicker walled arteries of other organs and tissues.

Our first idea, on finding the great influence on the volume of the brain of changes in the blood-pressure was, that this effect might be due mainly to changes in the calibre of the arteries and larger arterioles,

and that the flow of blood through the capillaries of the brain might not be influenced to a corresponding degree. As we have pointed out above, however, the character of our curves is opposed to this view. It may be mentioned also that Gärtner and Wagner[1], who measured the outflow from one of the intracranial veins, (the skull-cavity being unopened), found that this varies with the arterial pressure. They found that, when the arterial blood-pressure falls below 30-40 mm. Hg., the outflow of blood from the cerebral veins ceases entirely. One main factor, then, which influences the cerebral circulation, is the arterial pressure.

The great importance, for the economy as a whole, of a due supply of blood to the brain leads to a consideration of the question as to the manner in which the influences which modify the arterial pressure are affected by the requirements of the brain in the matter of blood-supply. It need hardly be said that the vasomotor nervous system, the cardiac nerves, the amount of blood in the body, and the intravenous pressure, are the prominent factors which are capable of influencing the arterial blood-pressure. The most fully recognized of these is the vasomotor mechanism.

Let us consider for a moment what is the relation of this to the cerebral circulation.

The vaso-constrictor centres may cause rise of the arterial pressure as a result of nerve impulses reaching them from the periphery of the body by centripetal nerve-fibres, and also as a result of direct excitation of the centres themselves. Let us take the latter case first.

Anæmia of certain parts of the brain may serve as a good example of a natural mode of excitation of the vasomotor centres. Such anæmia may be due to diminution of the arterial pressure, to local obstruction of the blood-vessels or to rise of the extra vascular pressure either locally, from e.g. tumour-growth, or affecting the whole of the intracranial cavity. In whatever way produced, anæmia of the central nervous system excites the vaso-constrictor nerves with the result that owing to constriction of the vessels of the digestive, urinary and other systems, the arterial blood-pressure rises, causing an increased flow of blood through the cerebro-spinal blood vessels.

The excitation of the vasomotor centres by anæmia is evidently, then, protective, an increased supply of blood to the central nervous system being obtained by sacrificing the blood-supply of certain other

[1] Loc. cit.

parts of the body whose functional activity can be temporarily diminished or arrested without serious harm to the economy as a whole.

In the excitation of the vasomotor centres by asphyxia the same protective interference with the blood-supply of certain organs is to be met with resulting in an increased flow of blood through the cerebral vessels.

So far as we know, the same explanation holds good for all cases, in which, as a result of interference with the nutrition of the cerebro-spinal axis, excitation of the vaso-constrictor centres takes place. We conclude, then, that when the vaso-constrictor centres are excited directly in the normal animal, by interference with the nutrition of the brain and spinal cord, the rise of the aortic blood-pressure which results is advantageous to the economy in that it increases the blood-supply of the central nervous system.

If this view be a correct one, we would expect to find centres which have the power of constricting certain of the systemic vessels, in order to raise the arterial pressure, situated at those parts of the cerebro-spinal axis which are of greatest vital importance to the economy as a whole. It need hardly be said that the respiratory centre is of greater vital importance than any other, and this we presume is the reason why the chief vaso-constrictor centre is placed so very close to it. We would expect, however, that other parts of the central nervous system which are of importance for the life of the individual would also have the power of calling into play the vaso-constrictor mechanism, when their nutrition is endangered. From this standpoint we may see some *raison d'être* for the various vasomotor centres which have been described as existing in the corpus striatum and elsewhere in the brain and spinal cord.

What can be said as to the relation between the requirements of the brain and the rise of arterial pressure which results from excitation of the vaso-constrictor centres by centripetal impulses? It need hardly be said that centripetal impulses, be they sensory or be they otherwise, would have no meaning were they not for the purpose of calling into activity those parts of the central nervous system for which they are destined. The connection between variations in the functional activity of any organ or tissue of the body and corresponding variations in the amount of blood which it requires is fully recognized by physiologists.

We conclude then that the rise of arterial pressure, which may result from certain centripetal nerve-impulses, is of

benefit to the economy by increasing the blood-supply of the central nervous system which is called into increased functional activity by the impulses in question, as well as by aiding the congestion of the part of the body whence the impulses are derived.

We now come to the much discussed question as to whether any centripetal nerves exist which are capable of influencing the blood-vessels of the brain directly, i.e. independently of changes in the general arterial or venous pressure. Our answer to this is, that we have diligently sought for such, and have found no evidence that vasomotor nerves for the brain are to be found outside the cerebro-spinal cavity. The positive results obtained by other workers on the cerebral circulation are derived from observations on the section and stimulation of one pair of nerves, viz. the vago-sympathetic of the dog or the cervical sympathetic of the rabbit or cat. These positive results, however, do not agree with one another. We ourselves also obtained results from section and stimulation of these nerves which were at first sight contradictory. We found, however, that those results were due to nerve influences descending the vago-sympathetic, and that they affected the cerebral circulation indirectly only, i.e. by the changes which they produced in the intra-venous pressure.

We found that this fact explained satisfactorily the discrepancies in our own results. It is also fitted to explain why other observers obtained the contradictory results which we have had occasion to refer to.

Under these circumstances we conclude that there is no reason for believing that vaso-motor nerves for the brain are to be found in the nerves of the neck, and that therefore there is no evidence of their existence outside the cerebro-spinal canal.

Are vasomotor nerves for the brain to be found in the medulla or in the spinal cord? We have found no evidence of the existence of such nerves. Direct stimulation of the medulla and cervical cord resulted only, in our observations on the subject, in passive arterial congestion.

Is then the supply of blood to the brain influenced only by changes in the general arterial and venous pressures? Our observations on the effect of various chemical substances on the cerebral circulation shew that the cerebral vessels can undergo active changes in calibre. An especially important instance of this is, we think, to be found in the influence on the volume of the brain of comparatively small doses of a free acid introduced into a vein. As we have pointed out, the

expansion of the cerebral vessels which is thereby produced, is not due to any passive distension of the cerebral arteries or veins resulting from increase of the arterial and venous pressures. In other words it must be looked upon as being the result of active expansion of the blood-vessels of the brain. This active congestion of the brain is too striking a characteristic of the cerebral circulation not to have forced itself strongly upon our attention,—the increase of the volume of the brain being great even when only small quantities of acid are injected.

The possible bearing of this fact on the mechanism by which the cerebral circulation is normally regulated, was too obvious to be overlooked. We could not help remembering the observations of Langendorf[1] and Gescheidlen on the chemical reaction of the grey substance of the brain. The former observer found, as will perhaps be remembered, that the grey—as well as the white—substance of the brain is normally alkaline in reaction, but that, even a few minutes only after extirpation of a portion of the grey substance it becomes acid. He found, also, that cerebral anæmia, produced by closure of the carotid and vertebral arteries, causes the cortex to give an acid reaction in a very short time, and that the acidity gradually disappears if the cerebral vessels be re-opened. These changes, therefore, in the reaction of the cortex must be looked upon as the result of vital, and not of cadaveric, chemical action. They are, there is reason for believing, due to the formation of (ethylidene) lactic acid.

The remarkable characteristics of the anatomy of the cerebral lymphatics, forming as they do complete sheathes round the arterioles of the brain, whose muscular walls come in direct contact with the lymph, could not but appear to us specially interesting when we sought to interpret the facts to which we have just referred. In order to further elucidate this subject, we thought it advisable to make the following experiment, the results of which are illustrated by Fig. 13, Pl. IV.

The experiment, which was made on a dog (A), was arranged so that on the same drum simultaneous tracings were recorded of the arterial pressure in the femoral artery, of the venous pressure in the subclavian vein, and of the volume of the brain. As a part of the preparation for the experiment, an extract of a portion of the brain of another dog (B) had been made in the following way:—some four hours after the animal (B) had been bled to death (the head having in the mean time been kept in an incubator at a temperature of 37 C.), the

[1] *Biolog. Centralblatt.*, 1886. S. 188.

brain was removed, and one of the hemispheres rubbed up in a mortar with about 250 c.c. of warm, normal, neutral salt solution.

The filtrate obtained from the emulsion thus prepared was used for injection into the vascular system of the animal (A). (The filtered fluid it may be mentioned gave a faint reddish tinge to blue litmus paper.) The injection was made slowly through a cannula tied in the submaxillary artery, the fluid being thus introduced into the common carotid.

Figure 13 shews the effect on the cerebral circulation of an injection of 3 c.c. of a brain-extract prepared in the manner above described. As can be seen in that figure the brain expanded immediately after the injection so greatly that the point of the oncograph lever was rapidly carried off the drum, there being no corresponding rise of either the arterial or venous blood-pressures. It is evident, then, that in a brain whose blood-supply has been arrested for some little time, there is a substance or there are substances which, when introduced into the circulation, are capable of causing active expansion of the cerebral vessels.

It is, we think, reasonable to suppose, in view of the facts above stated, that the cerebral congestion in this experiment is due to the action on the cerebral blood-vessels of the dog (A), of the products of cerebral metabolism, which had accumulated in the brain of the dog (B) from which the extract had been prepared. These facts seem to us to indicate the existence of an automatic mechanism by which the blood-supply of any part of the cerebral tissue is varied in accordance with the activity of the chemical changes which underlie the functional action of that part. Bearing in mind that strong evidence exists of localisation of function in the brain, we are of opinion that an automatic mechanism, of the kind just referred to, is well fitted to provide for a local variation of the blood-supply in accordance with local variations of the functional activity.

We conclude then, that the chemical products of cerebral metabolism contained in the lymph which bathes the walls of the arterioles of the brain can cause variations of the calibre of the cerebral vessels: that in this re-action the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity.

The probability, that the active congestion of the brain during asphyxia (to which reference has been made on pages 91 and 92), is due to this intrinsic mechanism, is, we think, an obvious one.

There are, then, two more or less distinct mechanisms for controlling the cerebral circulation, viz.—firstly, an intrinsic one by which the blood-supply of various parts of the brain can be varied locally in accordance with local requirements, and secondly, an extrinsic, viz.—the vasomotor nervous system, whose action affects the amount of blood passing through the brain in virtue of the dependence of the latter circulation on the general arterial blood-pressure. Presumably, when the activity of the brain is not great, its blood-supply is regulated mainly by the intrinsic mechanism and without notable interference with the blood-supply of other organs and tissues. When, on the other hand, the cerebral activity is great, or when the circulation of the brain is interfered with, the vasomotor nerves are called into action, the supply of blood to other organs of the body being thereby trenched upon.

There is, however, a third mechanism by which the cerebral circulation can be influenced and the importance of which, we are inclined to think, must be considerable. We refer to the effect on the cerebral vessels of changes of the general venous pressure which, as we have mentioned, may be greater in extent than is usually supposed. The volume of the brain varies with the pressure in the large veins, and it is impossible to overlook the fact that such changes in the pressure of the blood within the cerebral venous capillaries, which have extremely thin walls, must be of importance for the nutritive transudation taking place through those walls. As above stated, there are descending fibres in the vago-sympathetics which are capable of causing great changes in the pressure within the large intra-thoracic systemic veins.

In conclusion, let us refer to one or two points, connected with our subject, which are of interest to the pathologist.

The fact that, in all cases where the systemic blood-pressure is high, we have increased blood-supply to the brain, will explain why cerebral hæmorrhage is so frequently associated with conditions in which the aortic blood-pressure is raised.

The frequency of cerebral hæmorrhage and cerebral œdema in Bright's disease and in other affections of the renal system, where the blood-pressure is higher than normal, are examples of this relationship.

In cases of cerebral hæmorrhage, the physician, when called in after the seizure, very frequently finds the patient with a congested face and neck, with distended veins, and with a hard and slow pulse. The high arterial pressure and venous congestion of the brain, which are indicated by these signs, used to be looked upon as fitted to increase the escape

of blood from the ruptured vessel, and it may be that they do have that effect. There is no doubt, however, that they are due to the interference with the nutrition of certain vital parts of the brain, from the pressure of the effused blood; in other words that they are protective in the sense to which we have drawn attention above. If we seek to lower the arterial and venous pressures, by venesection or strong purgatives, we may certainly thereby diminish or stop the hæmorrhage, if it be still going on, but by so doing we run the risk of losing the patient's life by interference with a protective mechanism, on the efficient action of which the life of the patient possibly depends.

The same applies to any attempt to diminish the inflow of blood to the brain by compression of one or both carotids. There is, we think, small cause for surprise in the fact that venesection was found to increase the mortality after cerebral hæmorrhage. It certainly seems a pity that the vital parts of the brain cannot protect themselves against the inanition to which they are exposed by the pressure of the effused blood, without, at the same time, raising the pressure within the ruptured vessel.

The punctiform, and occasionally larger, hæmorrhages in the neighbourhood of foci of anæmic softening of the brain, are presumably due to the congestion which results from the action of the intrinsic vasomotor mechanism by which the cerebral blood-supply is regulated, and which, as above mentioned, is brought into play by anæmia.

The depressing effect of free alkalies as employed in medicine may, we think, possibly be explained by the anæmia of the brain which these substances produce.

Finally, a word may be said regarding the relation between the cerebral blood-supply and the rhythmic variations of the activity of the respiratory centre which produce the "Cheyne-Stokes" breathing. Curve 14, Pl. IV., which we copy from Gad[1], shews simultaneous tracings of the arterial pressure and of the respiratory movements. It was obtained from a rabbit, from which a certain amount of blood had been abstracted. As is mentioned by Gad, the Cheyne-Stokes breathing frequently occurs in rabbits which have been rendered anæmic by venesection. It may, we imagine, be safely assumed that, in cases where the blood-supply of the respiratory centre has fallen below that required to adequately meet its wants, its functional activity will necessarily vary with variations in the tide of blood circulating through it. In

[1] Gad. "Ueber Haemorrhagische Dyspnoë. *Du Bois' Archiv.* 1886. S. 513.

Curve 14, it can be seen that the blood-pressure shews that rhythmic rise and fall which constitute what are generally referred to as "Traube-Hering" waves.

It can be seen that, with each successive rise of the arterial pressure, the extent of the respiratory movements increases—diminishing on the other hand with each descent. As is mentioned by Gad, the characters of the respiratory tracing in this curve indicate that there is a rhythmic variation of the excitability of the respiratory centre and not a rhythmic variation of the excitation of that centre, which latter was held by Filchne to be the cause of the "Cheyne-Stokes" breathing. The cause of the rhythmic increase and decrease in extent of the respirations may reasonably, we imagine, be explained as due to the rhythmic variations of the blood-supply of the respiratory-centre which necessarily result from the "Traube-Hering" blood-pressure waves.

Traube-Hering curves of the arterial pressure are of common enough occurrence in man, as well as in certain of the lower animals. It is probable, we think, that the rhythmic variations in the acuity of auditory and visual perception, of which many of us have had personal experience, are due to Traube-Hering undulations of the arterial pressure—with the wave-length of which they very well agree.

October, 1889.

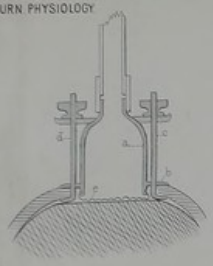

Fig 1.

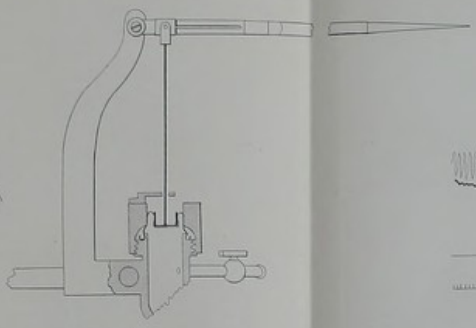

Fig 1a.

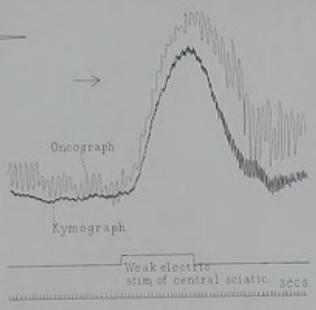

Fig 2

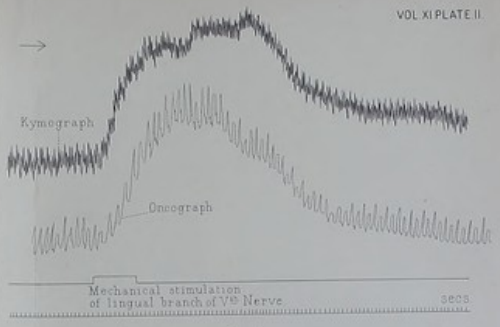

Fig 3

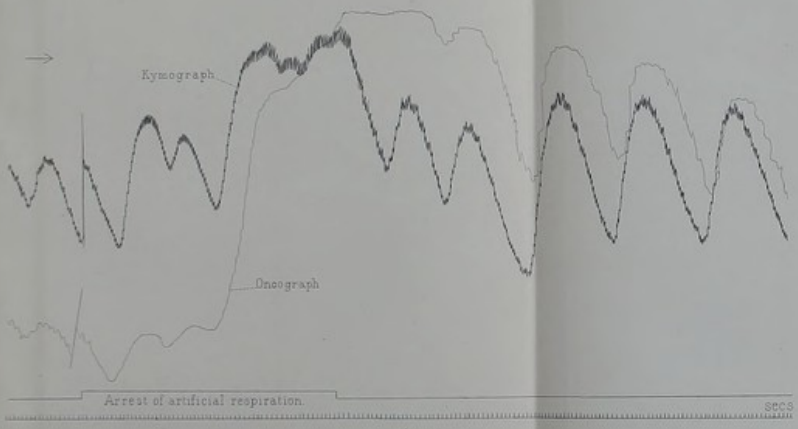

Fig 4.

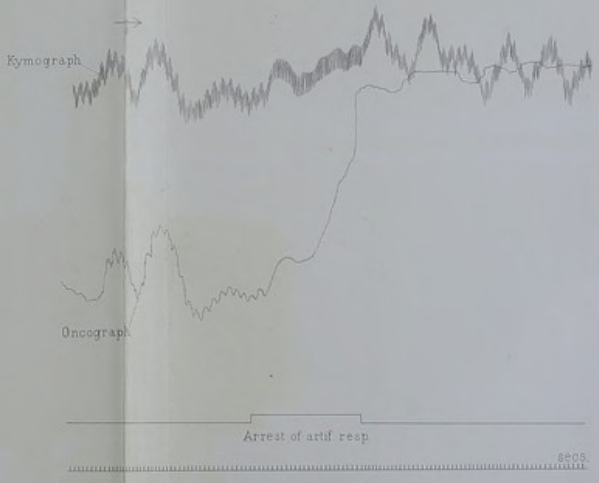

Fig 5.

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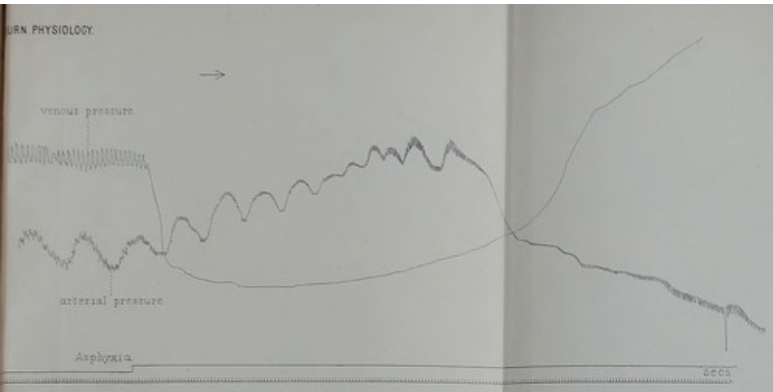


Fig 6.

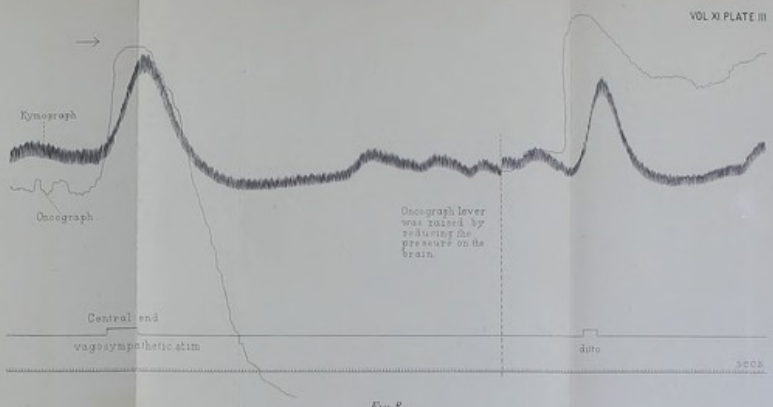


Fig 8.

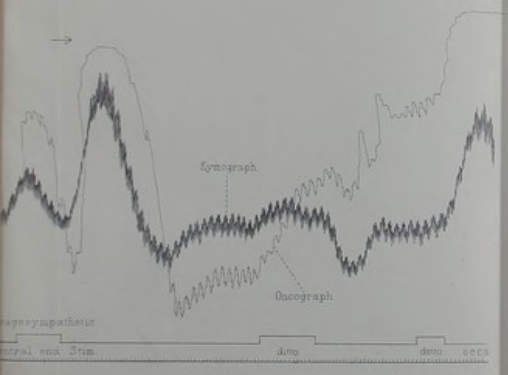


Fig 7

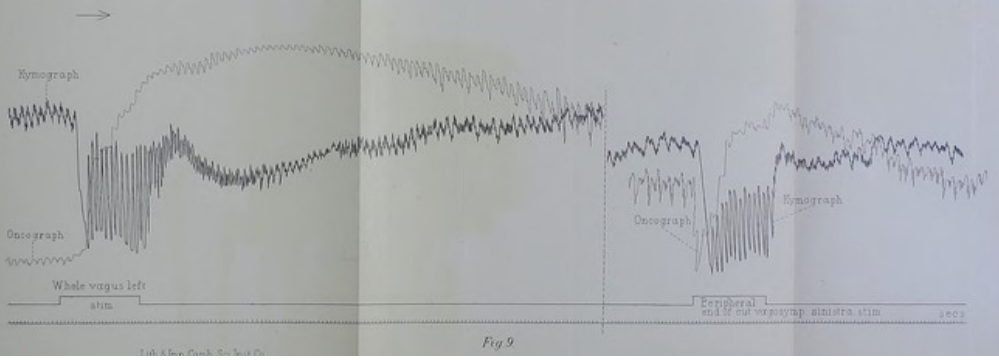
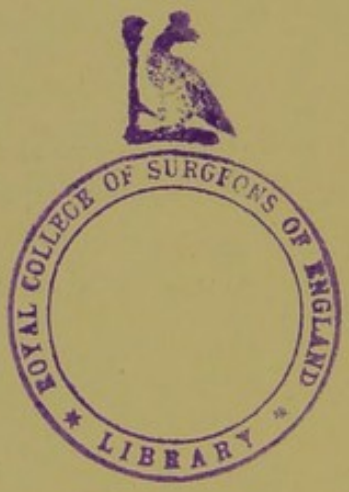


Fig 9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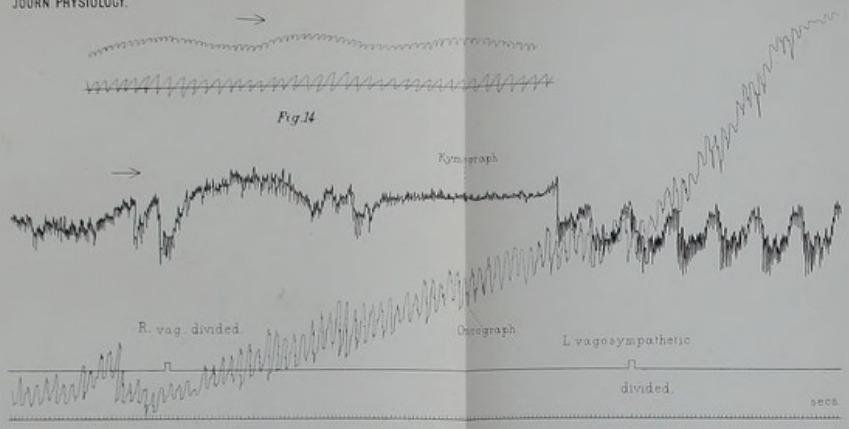
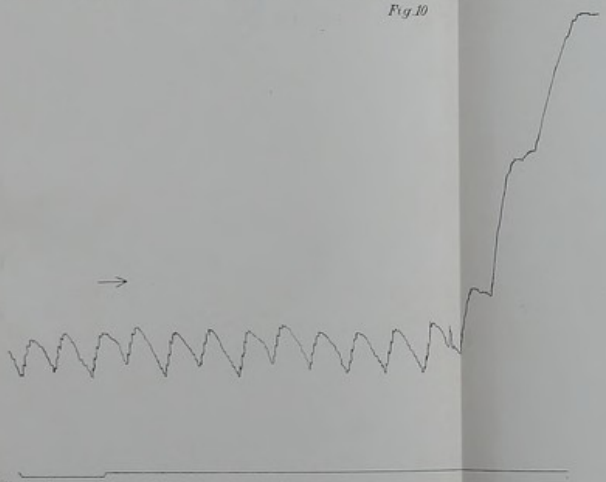


Fig. 14

Fig. 10



½ ccm. Liq. Strychnia. P. B. injected. Fig. 11

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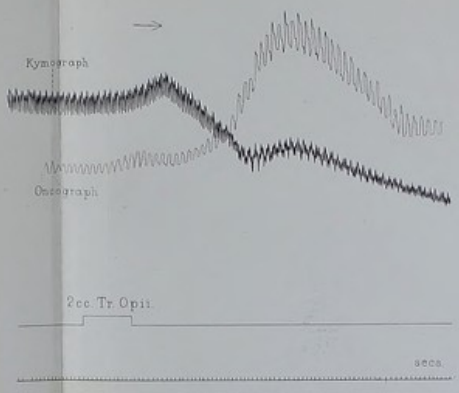

Fig. 12

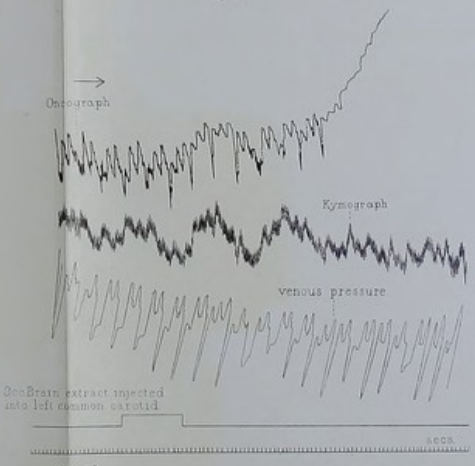

Fig. 13


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