A contribution to our knowledge of the physiological action of antipyrin / by Rayner D. Batten and T.J. Bokenham.

[Reprinted for the Author from the BRITISH MEDICAL JOURNAL, June 1, 1889.]

A CONTRIBUTION TO OUR KNOWLEDGE OF THE PHYSIOLOGICAL ACTION OF ANTIPYRIN.

BY RAYNER D. BATTEN, M.D., B.S.LOND.,
AND
T. J. BOKENHAM, L.S.A.LOND.
(From the Laboratory of Dr. Lauder Brunton.)

THE subject of the physiological action of antipyrin was originally taken up by us in order to find out in what manner the drug might act in migraine and kindred diseases. The true pathology of these disorders being uncertain, the subject was, of course, a complex one, and we had no little difficulty in deciding on a definite plan of research. Most physicians have, however, observed that the attacks are often accompanied by an alteration in the tone of the vascular walls—namely, an irregular contraction or spasm of portions of one of the temporal arteries, and probably of others less superficial. We thought, therefore, that here might be a clue to the action of the drug, which has been observed to abolish this symptom. To test this view it was suggested by Dr. Lauder Brunton that we might obtain some information by repeating Nothnagel's experiment of locally stimulating the exposed intestine of an animal by means of a crystal of sodium salt, this producing, under normal circumstances, a distant peristaltic contraction towards the duodenum, as well as a local annular constriction at the point of stimulation.

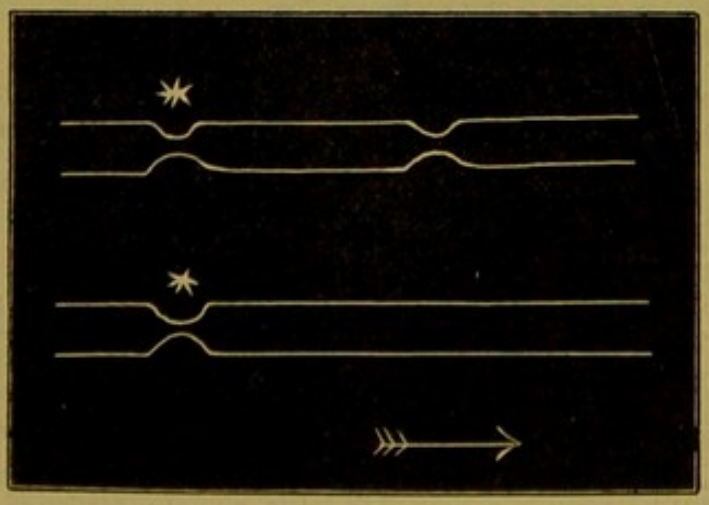


Diagram illustrating the effect of stimulating the intestine of an animal with a sodium salt; A before, B after the injection of antipyrin. The arrow points towards the duodenum. * the point of application of the sodium salt.

Now, certain drugs, for example, morphine, have been found to alter this phenomenon, that is, to interfere with the transmission of the stimulus along the intestinal nerves from the point of irritation, and we find that antipyrin acts in this way. It is possible that its action in removing the contraction of the unstriped muscle-fibre of the blood-vessel is of a similar nature.

A cat was placed under ether, tracheotomised, and a cannula inserted in the external jugular vein; the abdomen was opened in the median line, and the animal placed in a bath of saline solution. A soda salt was then applied to the intestine with the usual result.

After injecting one gramme of antipyrin in solution, we found that we were unable by application of the sodium salt to produce anything more than a local annular contraction.

Following out this view, we made some experiments to ascertain the influence of the drug on the normal contraction of muscle, voluntary and involuntary. Our results in this direction were, however, entirely negative, weak solutions having no effect on the contractility, and strong solutions only causing the death of the preparation—in fact, acting simply as a saline solution of similar strength.

We next turned our attention to the effect on the walls of the arterioles, causing the drug to circulate through the vessels of a frog, whose brain and spinal cord were destroyed, and so prepared that fluid entered by one cannula in the aortic bulb and escaped by another inserted into the vena cava inferior. The rate of flow through the vessels was estimated by the number of drops which issued per minute from the vena cava. Each drop as it fell was made to break an electric circuit, in which was also a recording magnet. We were unable, however, to detect any difference in the rate of escape—and thence in the constriction or relaxation of the arterial walls—whether simple Ringer's solution[1] or Ringer's solution containing antipyrin in various proportions was circulated.[2] Hence, we conclude that any controlling influence over muscular action is exerted—not directly, but indirectly—through the nervous system.

According to the researches of H. C. Wood, Reichert, and Hare, no effect is produced on the normal blood-pressure in dogs when antipyrin is introduced into the circulation. Coppola, however, states that blood pressure is slightly raised, the frequency and force of the heart being increased.

Local Action on Motor Nerves.—As regards the local action of the drug on motor nerves, we find that both conducttivity and irritability are destroyed, the former being earliest affected.

General Action.—To test the general action of antipyrin, we made some experiments on normal frogs, guinea-pigs, rats, and rabbits, injecting the drug dissolved in saline solution into the dorsal lymph sac or peritoneal cavity, and also administering it by the stomach. The results obtained showed that the drug had a decided toxic effect, the symptoms being evidently referable to the brain and spinal cord. The course of symptoms of poisoning

---

[1] Ringer's solution consists of saline solution, 0.75 per cent., made with tap-water with a trace of potassium chloride, that is, 12 cubic centimètres of a 1 per cent. solution in 800 cubic centimètres.

[2] This result is not in accord with those of Coppola (*Annali di Clinica Med. Farmaceut. e di Farmacologia*, January, 1885), who found that in the excised lungs of a dog, through which either blood, or blood *plus* antipyrin, could be circulated by means of a Marriotte's bottle, a great dilatation of the vessels took place on causing the drug (1 per cent. solution in defibrinated blood) to pass through them. We hope to make this question, together with some other points, the subject of a future paper.

was much the same in all the animals experimented upon, though the predominance of special symptoms varied in different cases.

In the frog, a stage of dulness and quiet was followed by inability to direct its movements—that is, after hopping it frequently fell on its side. In a further stage, the animal, when laid on its back, remained quite still in that position, making no attempt to regain its normal sitting posture. It would respond to slight stimuli, not by efforts to escape, but by an apparently purposeless extension of the legs. When compared with the results obtained from Goltz's experiments, in which he removed successively the cerebral lobes, optic lobes, cerebellum, and medulla oblongata, it would seem that antipyrin acts in a similar manner, causing paralysis of these parts progressively, from before backwards.

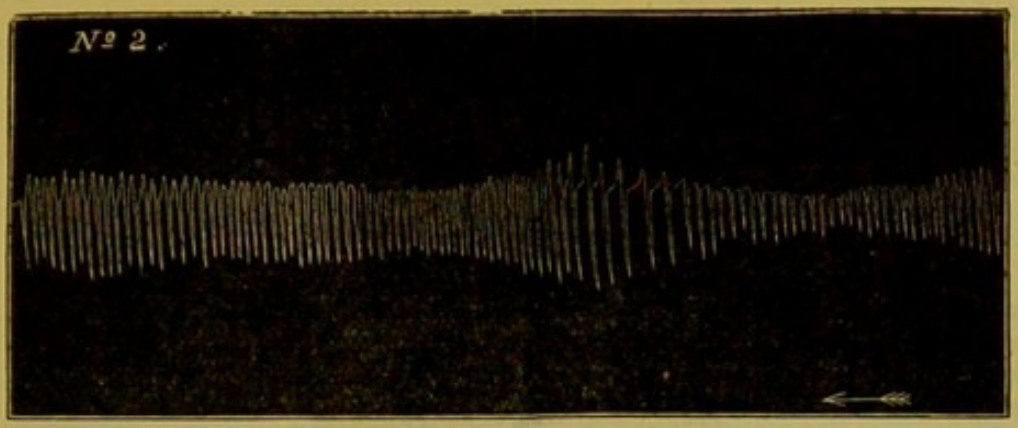
In guinea-pigs and rats, the onset was usually marked by an impairment of voluntary movement, and increasing unsteadiness, the animal standing still and swaying from side to side, often at the same time shaking violently. This condition would proceed till the animal was no longer able to maintain its balance, and fell on its side.

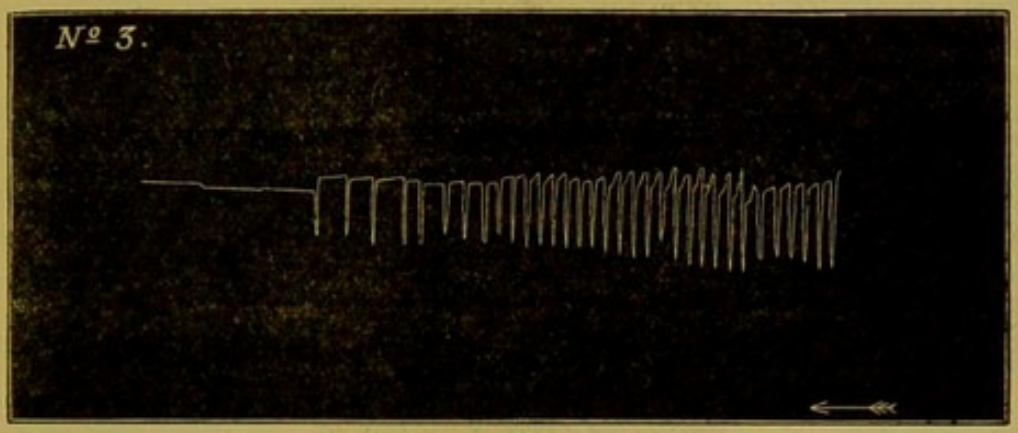
The most marked early symptom, common to all classes of animals experimented on, was rigidity of certain sets of muscles. In frogs this usually began in the fore limbs and extended to the muscles of the back or abdomen, causing marked opisthotonos, pleurosthotonos, or emprosthotonos; while in the guinea-pig the hind limbs would become suddenly extended and rigid, so that the animal, on attempting to walk, did so only with its fore limbs. The rigidity afterwards extended to the other limbs, the head being also drawn right back into a position of extreme extension on the spine.

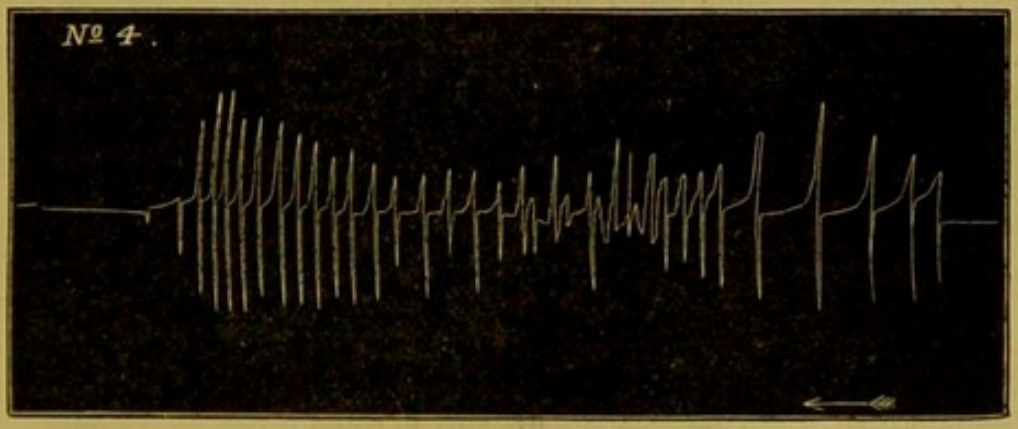
This rigidity was followed in mammals by peculiar rhythmic movements, the limbs moving very rapidly backwards and forwards, as if the animal were running, although it was, of course, on its side. In one or two instances we observed that the animal sometimes regained the use of its fore limbs, the hind legs being still somewhat stiff. It then performed circus movements, always in the same direction, the motion being caused almost solely by the fore limbs round the hinder ones as a centre. These rhythmic movements alternated with the rigidity, and the animal then passed into a stage in which the rigidity, although still present to some extent, no longer formed so marked a symptom, and a condition of extreme irritability came on, so that a slight tap caused the limbs to be shot out in spasm. In more severe cases, even a draught of air, or the vibration caused by walking about in the room, was sufficient to produce a series of convulsive spasms over the whole body. This latter effect was noticed in rats and frogs. In the latter, it would persist often for more than twenty-four hours, while in the former it seldom lasted for more than one or two hours. In the other animals experimented on, either the irritability became less and less, and they recovered, or they gradually passed into a paralytic state, respiration becoming slow, laboured, and spasmodic, and death ensued.

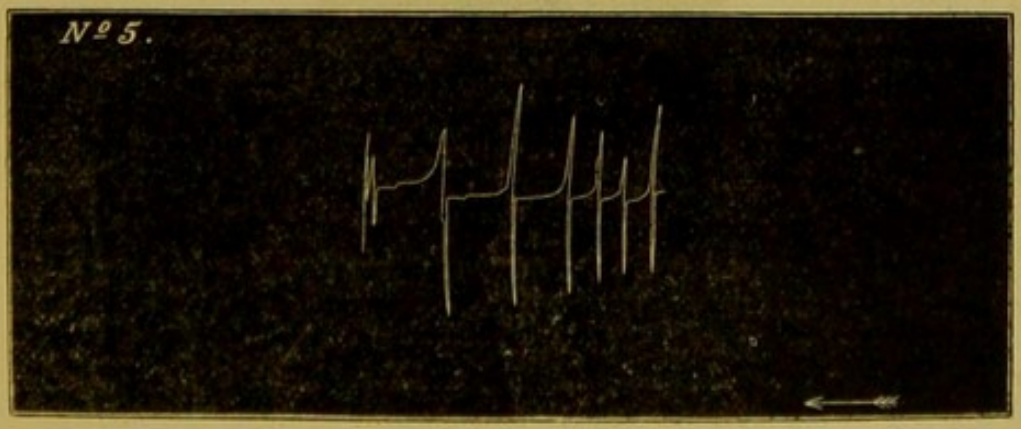
To ascertain whether the symptoms were of spinal or cerebral origin, we divided the cord below the medulla, in a frog which already exhibited symptoms of poisoning, with the result that the symptoms were abolished only temporarily, to reappear after an interval. To control this result, we divided the cord of a second frog in the middle, and then poisoned. Symptoms then appeared in the parts of the body both before and behind the lesion. It is


Nº 1.


№ 2.


№ 3.


№ 4.


№ 5.

fair therefore to conclude that the convulsions in frogs are of spinal, not of cerebral, origin.

Action on Respiration.—Respiration seems to be the most profoundly affected of all the vital functions, and it is probable that its failure is, in fatal cases, the cause of death. Our observations were made on cats, rats, and guinea-pigs. The following may be taken as an example of the method of experimenting, results in other instances being strictly comparable.

Ether was given and tracheotomy performed. To the tracheal cannula a three-way tube was attached, the anæsthetic being given by one limb, while the other was connected with a Marey's recording tambour, the lever of which registered on a slowly revolving recording drum.

Guinea-pig; weight, 530 grammes; temperature 38.5° C.; 0.25 gramme of antipyrin (10 per cent. solution) injected into peritoneal cavity. In three minutes respiration was slower (Tracing 1). Temperature 29.5° C. Respiration rapidly became more involved and irregular (Tracing 2), and ultimately ceased. Artificial respiration was commenced, and after some minutes natural breathing returned, the rhythm being much slower. At fifty minutes a further dose (0.125 gramme) was injected, after which breathing became still slower, very shallow, and with frequent stoppages (Tracings 3, 4, 5), during which artificial respiration was resorted to. Towards the end of the experiment breathing was curiously spasmodic and irregular, and at length (one hour fifty minutes) the animal died. At times during the experiment the rhythm coincided with that of Cheyne-Stokes breathing.

Influence of Anæsthetics.— In the course of our experiments the influence of anæsthetics on the action of the drug was at times noteworthy. We therefore made some special experiments with a view to a closer study of this point. Two methods of investigation were adopted: 1. We produced symptoms of poisoning in an animal (rat or guinea-pig), and then administered an anæsthetic. 2. We produced profound anæsthesia, and then attempted to produce symptoms by injection of the drug. By the first method it was found that administration of an anæsthetic entirely abolished all muscular symptoms of poisoning, but that these reappeared on recovery from the anæsthetic. By the second method, although temperature and respiration were much affected, we found no other indication of poisoning.

The following three experiments may be taken as examples.

Experiment I.—Rat (weight 70 grammes). Room temperature 22° to 24° C. Under chloroform, 0.1 gramme antipyrin dissolved in normal saline solution was injected into the peritoneal cavity. Temperature of animal 35.5° C. Respiration soon became laboured and slow. The anæsthetic was then discontinued, when the respiration became spasmodic. Chloroform was resumed, with the result that the respirations became more regular. This part of the experiment was repeated several times, with the same result. Body temperature after one hour had fallen to 27° C. Symptoms of poisoning, as rigidity of limbs and great irritability—the latter so marked that a draught of air would cause a tetanic spasm of the whole body—were very striking in their occurrence whenever the anæsthetic was discontinued, but were entirely abolished by a few inhalations of chloroform. After two hours thirty minutes symptoms were less severe, and body temperature was 32° C., and shortly after the animal quite recovered.

Experiment II.—Symptoms of acute poisoning were produced in a rat, and administration of chloroform was found to entirely abolish them. Details of experiment similar to those recorded in Experiment I.

Action of Antipyrin on Frogs Immersed in Water at Various Temperatures.

No. 1.—Temperature, 12° C.		No. 2.—Temperature, 4° C.		No. 3.—Temperature, 25° to 35° C.	
Time after Injection.	—	Time after Injection.	—	Time after Injection.	—
hrs. mins.		hrs. mins.		hrs. mins.	
—	Injected mviii of 5 per cent. solution of antipyrin into posterior lymph sac.	—	Injection as in No. 1.	—	Injection as in No. 1.
0 5	After efforts to escape, it fell on its back, and remained in that position. Legs were drawn up and the whole body rigid.	—	During immersion in water, at this low temperature, it exhibited no symptom save those of a normal winter frog.	—	Frog almost immediately became flaccid, and apparently dead.
0 35	Animal lies on abdomen, its limbs rigid, fore limbs extended, hind legs flexed at side of body. A slight tap produces sudden extension of the hind limbs.			0 11	Fore limbs quite rigid, hind limbs undergo slight convulsive movements on being touched. Animal appears sluggish.
0 40	Symptoms still more marked. Emprosthotonos follows slight taps even on the containing vessel.	0 47	Animal removed to water at 14° C.	0 19	Temperature 31.5° C. Animal very irritable.
1 10	Emprosthotonos and pleurosthotonos well marked; other symptoms very distinct.	1 22	Exhibits slight symptoms of poisoning.	0 20	Animal became quite flaccid, and does not respond to stimuli. Removed from bath.
2 20	Animal in state of extreme irritability. The slightest stimulus, such as blowing, or moving about the room, produces violent clonic convulsions.	2 22	Absence of voluntary movements; diminished irritability, and commencing rigidity of fore limbs.	0 24	Irritability returned, and more marked than before.
				0 34	Irritability still exaggerated. No opisthotonos.
				2 19	Condition similar to No. 1.
—	February 6th.—Frog still somewhat irritable, legs somewhat stiff, and it does not recover immediately when turned on its back.	—	February 6th.—Irritability still increased, fore limbs stiff, the animal makes no spontaneous movements.	—	February 6th.—Seems to have quite recovered.

EXPERIMENT III.—The same procedure was adopted in the case of a guinea-pig, the result being exactly similar. Ether was used instead of chloroform.

Influence of Temperature.—The effect of external heat and cold on the action of the drug in frogs seems remarkable, and to some extent resembles that of picrotoxin. It was demonstrated as detailed in the following experiments. It will be noticed that heat brings on the paralytic stage in frogs almost immediately, whereas cold apparently delays indefinitely the appearance of any symptoms whatever. Not only so, but even after the extreme action of the drug has been produced by heat, the application of cold reduces its effect, and causes symptoms to appear characteristic of an earlier stage of poisoning, such as rigidity and spasms.

Anæsthetic Action.—As regards the power of conduction of sen sory nerves, and the transmission of peripheral stimuli through the cord, it has been already remarked that draughts of air are sufficient to cause convulsions in frogs and rats. This would seem to indicate an increased perceptibility for at least some sensory impressions. We found, however, that painful stimuli, such as pinching or pressing, or even wounding with a sharp point, were absolutely without effect in producing convulsions, although they were at once produced by a sudden slight touch on the skin, even with the end of a bristle.[3]

Summary.—From the foregoing experiments and observations on the action of the drug we conclude that its main, if not its sole, action is due, directly or indirectly, to its influence on the nervous system. It appears to act on all parts of it—mainly on the spinal cord, but also on the brain and motor nerves.

We have not yet found any means of absolutely satisfying ourselves as to the tracts of the spinal cord which are specially affected by antipyrin, but if it is fair to compare the symptoms produced by a drug with those the result of disease, then we can show that the localisation of the action of antipyrin is fairly obvious.

The symptoms in question bear a very strong resemblance to those of lateral sclerosis, and we therefore think that the action of the drug may be localised in the lateral columns of the cord. For instance, we found in guinea-pigs and a cat spastic rigidity of the hind limbs, and, in all animals experimented upon, rigidity formed a marked symptom. Further, in the first mentioned animals this symptom appeared to come on with any attempt to use the limbs, just as is the case with a patient with lateral sclerosis.

The excess of myotatic irritability is also very marked, the slightest tap being sufficient to evoke violent muscular contractions, and in extreme cases to cause clonic spasms of the whole body. In one experiment phenomena exactly similar to those of ankle clonus were obtained.

In all cases the contrast between the effect of painful stimuli and stimuli such as the slightest taps, or even the vibrations produced by walking about the room, was most marked, the former producing less effect than in a normal animal, while the latter caused the violent spasmodic movements already mentioned.

The localisation of the action of drugs on the different tracts of the spinal cord appears to be a field of research in which, as yet, little has been done, and is one that gives promise of very in-

[3] Somewhat the same result has been noted in strychnine poisoning, in which touching the skin causes convulsions, but irritation of the skin by acid does not. (*Vide* Eckhard, Hermann's *Handbuch d. Physiol.*, Bd. ii, H. 2, p. 43).

teresting and useful results. In the present instance, the effects of the drug (antipyrin) are so transient, seldom extending over more than a few hours, and the recovery is so complete, that pathological results demonstrable by the microscope could hardly be expected. It is rendered more difficult from the fact that doses sufficient to cause death produce other symptoms not referable to the lateral columns alone.

Up to the present, as far as we are aware, the only instances in which definite changes have been found are the results of von Tschisch,[4] who by using certain drugs was able to show vacuolation of the cells of certain tracts of the nervous system. It is true that in cases of ergotism, caused by the continual consumption of rye bread containing ergot, there has been observed sclerosis of the postero-lateral columns, with corresponding symptoms during life; but to what extent this can be attributed to the action of the drug alone is uncertain, as other influences (famine, etc.) were at the same time at work, and similar results have not been obtained by the prolonged administration of the pure drug.[5]

With the haloid derivatives of the benzene group, Brunton and Cash[6] have observed symptoms showing the brain and spinal cord to be affected, and "giving rise to general tremors on movement resembling that observed in disseminated sclerosis" Sometimes, too, the tremor was observed independently of movement. The same two observers also found that amido-benzene caused symptoms like locomotor ataxy in frogs. They made many attempts to produce the changes permanently, but the symptoms passed off after elimination of the drug.

Such is the present position of the subject. The importance of being able to localise the action of a drug to a special tract of tissue cannot be over-estimated, and if further work should prove this to be possible it will go far to render the use of drugs in diseases of the nervous symptom a more rational proceeding.

As regards the action of antipyrin on the brain of mammals, but little can be said at present. From the rapid rhythmic movements noticed in many cases, and from the circus-movements sometimes observed, it may be concluded that either the motor centres themselves are involved, or that their inhibitory power is abolished. As regards the brain of frogs, we have recorded much more definite results in the early portion of the paper.

Clinically we sometimes meet with cases of poisoning by antipyrin, and it is interesting to observe that here also the symptoms are mainly nervous. In three cases observed by one of us, the symptoms were great restlessness, anxiety, and giddiness, the patients complaining also of "pins and needles" in the legs and feet. In another case, a girl taking 3 grammes daily for chorea became on the third morning drowsy, giddy, and finally delirious, with laboured, slow breathing, these symptoms lasting for about five hours. Dr. Jennings also records a case in which a maniacal condition followed the administration of large doses of the drug. It is striking how closely many of these symptoms resemble those which we have been able to produce in animals.

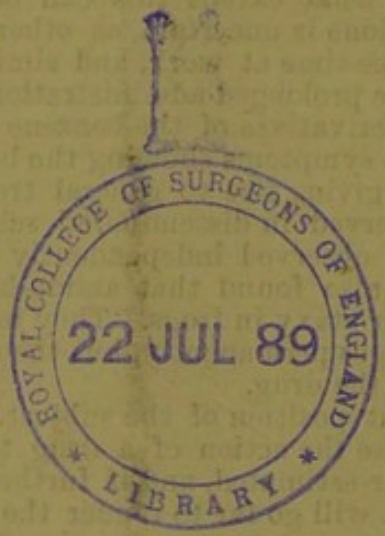
The foregoing research was conducted in the laboratory of Dr. Lauder Brunton at St. Bartholomew's Hospital, and to him we owe our very warm thanks for the use of it, and still more for his kindness in aiding us at all times with his advice and suggestions as to means of procedure.

---

[4] *Virchow's Archiv*, Band 100, p. 147.

[5] Ergotinic acid and cornutine, an alkaloid of ergot, give rise to spinal symptoms, but these are not referable to any definite area of the cord.

[6] *Proc. Roy. Soc.*, vol. 42, p. 240.


ROYAL COLLEGE OF SURGEONS OF ENGLAND
22 JUL 89
LIBRARY